Reward processing as a framework for studying symptoms of schizophrenia: a functional imaging approach

Dissertation
submitted to the
Faculty of Business, Economics and Informatics
of the University of Zurich

to obtain the degree of
Doktor der Neuroökonomie, Dr. sc.
(corresponds to Doctor of Neuroeconomics, PhD)

presented by

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approved in October 2015 at the request of
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The Faculty of Business, Economics and Informatics of the University of Zurich hereby authorizes the printing of this dissertation, without indicating an opinion of the views expressed in the work.

Zurich, 21.10.2015

The Chairman of the Doctoral Board: Prof. Dr. Todd Hare

Acknowledgments

First of all, I would like to thank Philippe Tobler and Stefan Kaiser for giving me the opportunity to pursue my PhD studies at the Faculty of Business, Economics and Informatics of the University of Zurich, and the Department of Psychiatry, Psychotherapy and Psychosomatics at the Psychiatric Hospital of the University of Zurich. During the three years of my doctoral studies I always felt their support and goodwill. The completion of this dissertation would not have been possible without their guidance. They fostered my development as a researcher and always encouraged me to push my limits. Furthermore, I would like to thank Martin Bischof, Matthias N. Hartmann-Riemer, Matthias Kirschner, Agne Kluge, and Boris Quednow for their support.

Contents

Abstract

Schizophrenia is an extremely debilitating psychiatric disorder that causes a drastic reduction in quality of life and strong impairments in social and occupational functioning. Patients with schizophrenia experience a broad spectrum of symptoms, among others, apathy and diminished expression (called negative symptoms) as well as delusions, hallucinations, and disorganized thoughts (called positive symptoms). The current understanding of the etiology of schizophrenia is a multifactorial model, with the factors genetics, neurodevelopment and environment. With regard to neurochemical abnormalities, a dysregulation in the dopaminergic system is proposed as primary pathology. The dopamine hypothesis of schizophrenia suggests that positive symptoms are linked to an excess of dopamine in the mesolimbic system, and negative symptoms are linked to a hypodopaminergic function in the mesocortical system (Kapur, 2003).

Dopamine also plays a pivotal role in reward processing. Recent evidence suggests that particularly learning and wanting, which are proposed as two out of the three main behavioral functions of reward, are mainly mediated by dopamine. The behavioral function of wanting implies that rewards serve as motivational magnets that attract us, lead to approach behavior and let us invest additional effort. The function learning implies that rewards induce changes in observable behavior and serve as positive reinforcers by increasing the frequency of behavior associated with the receipt of a reward. The evidence of dopamine's role in wanting and learning, combined with its implication in the etiology of schizophrenia, led to increased interest in studying the symptomatology of schizophrenia within a reward processing framework. The aim of this dissertation is to contribute to this effort by further elucidating how disturbances in specific reward processes relate to the pathophysiology and symptomatology of schizophrenia.

In study 1 (chapter 2.1. & appendix A) we are clarifying the specific associations of the two negative symptom factors apathy and diminished expression with deficits in reward anticipation, which is considered a subcomponent of wanting. To operationalize reward anticipation, we applied a variant of the monetary incentive delay task where rewards are not probabilistic, but dependent on the subjects' individual performance. We argue that this operationalization serves better to simulate goal-directed behavior. For the first time we could show that ventral striatal activity, which plays a pivotal role in reward anticipation, is inversely correlated with apathy, but not with diminished expression. This correlation implies that apathy reflects – among other factors – reduced wanting of a reward, which leads to a reduction in approach behavior and hence, reduced goal-directed behavior. Furthermore, the specific correlation of ventral striatal activity during reward anticipation with apathy supports the notion that the two negative symptom factors have specific underlying neurobiological mechanisms.

In the second study (chapter 2.2 & appendix B), we are elucidating a tonic form of reward anticipation, i.e., how the prospect of a reward modulates behavior during an extended period of time. We were particularly interested in how incentives change cognitive performance since the acquisition of most rewards in everyday life depend on the investment of cognitive effort. Although negative symptoms have been implicated with deficits in reward anticipation and cognition, no study ever elucidated the interaction between the two domains on a neurobiological level. We applied a well-known working memory task and varied the incentive for performance. When cognitive effort was rewarded compared to when it was not rewarded, we found – among other regions – activity in the rostral anterior cingulate (ACC). The ACC is considered to act as a hub region that links motivation and cognition, thereby controlling the demand of processing resources. We did not find any significant group difference between patients and healthy controls, which indicates that these groups do not differ in how they integrate information about prospective rewards and how they utilize this information in order to increase their performance. However, we found that the enhanced ACC activity in patients is inversely correlated with the negative symptom factor diminished expression. This is in line with the cognitive resource limitations model of diminished expression proposed by Cohen (2012). However, we expand Cohen's model by arguing that diminished expression is not solely caused by limited cognitive resources, but also by the inappropriate modulation of these resources. Additionally, we are the first group to propose a potential neurobiological model of diminished expression.

In the third study (chapter 2.3 & appendix C), we are elucidating whether patients with schizophrenia show deficits in reward representations. Since most representations of rewards are not inherent, they have to be learned at first. Hence, the representation of rewards can be considered the result of a learning process. A crucial mechanism for encoding rewards is the context specific adaptation of neural sensitivity. In order to encode an unlimited number of rewards with a limited number of neurons, neurons adapt their firing range to the currently available rewards in the environment. This ensures that reward sensitive neurons always exploit their entire firing range, which guarantees optimal discriminability between different reward amounts and hence, an accurate and precise representation of reward information. Although various studies have implied that deficits in reward representations could be the cause of reinforcement learning deficits, alterations in effort-cost computation, or deficits in associative learning, no study ever elucidated adaptive coding in patients with schizophrenia. For the first time, we show that patients with schizophrenia have deficits in the adaptation of neural sensitivity to the current reward context, which suggests that their reward representations are imprecise. We argue that this deficit could lie at the root of many dysfunctional reward processes, since an accurate representation is a prerequisite for any process that includes reward information. Furthermore, we provide evidence that this deficit is related to the general symptom severity, which suggests that this deficit could reflect a more basic dysfunction of schizophrenia instead of a specific symptom correlate.

In sum, we found evidence that specific reward-related processes, i.e., tonic and phasic forms of reward anticipation and adaptive coding of reward information, are correlated with symptoms of schizophrenia. This shows that abnormalities in reward processes, which are all mediated by dopamine, have the potential to offer insight into the symptomatology and the underlying neurobiology of schizophrenia. This holds promise for developing more targeted and efficient treatments. The results of this dissertation also support the increased effort in using reward processing as a transdiagnostic framework for studying hedonic deficits, motivational impairments, and learning deficits in other psychopathological disorders, such as major depression and bipolar disorder.

Zusammenfassung

Die Schizophrenie ist eine extreme beeinträchtigende psychische Krankheit, die eine drastische Reduktion der Lebensqualität und eine starke Einschränkung des Sozial- und Berufslebens zur Folge hat. Patienten mit einer Schizophrenie leiden unter einem breiten Spektrum an Symptomen, unter anderem an Apathie und reduziertem Ausdruck (genannt Negativsymptome) sowie an Halluzinationen, Wahnvorstellungen, und Denkstörungen (genannt Positivsymptome). Das aktuelle Verständnis der Ätiologie der Schizophrenie basiert auf einem multifaktoriellen Modell mit den Faktoren Genetik, neuronale Entwicklung und Umwelt. In Bezug auf neurochemische Abnormitäten wird eine Dysregulation des dopaminergen Systems als primäre Pathologie propagiert. Die Dopaminhyopthese der Schizophrenie legt nahe, dass Positivsymptome durch einen Exzess an Dopamin im mesolimbischen System verursacht werden, während dem Negativsymptome auf einer hypodopaminergen Funktion des mesocorticalen Systems basieren.

Dopamin spielt auch bei der Verarbeitung von Belohnung eine entscheidende Rolle. Neuere Beweise gehen davon aus, dass insbesondere Lernen und Wollen, welche als zwei der drei Hauptverhaltensfunktionen von Belohnung gelten, stark durch Dopamin moduliert werden. Die Funktion Wollen wiederspiegelt, dass Belohnungen motivationale Magnete sind, die uns anziehen, Annäherungsverhalten auslösen und uns zusätzliche Anstrengungen investieren lassen. Die Lernfunktion bedeutet, dass Belohnungen beobachtbare Verhaltensänderungen herbeiführen und Verhalten positiv verstärken, das in einer Belohnung mündet. Die Erkenntnis, das Dopamin im Wollen und Lernen eine wichtige Rolle spielt, kombiniert mit der ätiologischen Bedeutung Dopamins in der Schizophrenie, haben zu einer Zunahme des Interesses geführt, die Symptomatik der Schizophrenie im Rahmen der Belohnungsverarbeitung zu betrachten. Ziel dieser Dissertation ist es, diese Bemühungen zu unterstützen und genauer zu untersuchen, in welchem Zusammenhang spezifische Störungen in der Belohnungsverarbeitung mit der Pathophysiologie und Symptomatik der Schizophrenie stehen.

In Studie eins (Kapitel 2.1 & Appendix A) verdeutlichen wir den spezifischen Zusammenhang der beiden Negativsymptomfaktoren Apathie und reduzierter Ausdruck mit Defiziten in der Belohnungsantizipation, welches eine Subkomponente des Wollens ist. Um die Belohnungsantizipation zu operationalisieren haben wir eine Variante der Monetary Incentive Delay Aufgabe verwendet, in welcher die Belohnung nicht probabilistisch ist, sondern vom individuellen Verhalten der Teilnehmer abhängt. Wir glauben, dass diese Operationalisierung besser dazu dient, zielgerichtetes Verhalten zu simulieren. Wir zeigen zum ersten Mal, dass

die Aktivität im ventralen Striatum, welches bei der Antizipation von Belohnung eine entscheidende Rolle spielt, invers mit dem Faktor Apathie korreliert, und nicht mit dem Faktor reduziertes Verhalten. Diese Korrelation legt nahe, dass Apathie – unter anderem – auf ein reduziertes Wollen einer Belohnung zurückzuführen ist, welches zu einer Reduktion von Annäherungsverhalten und zielgerichtetem Verhalten führt. Zudem unterstützt die spezifische Korrelation der Aktivität im ventralen Striatum während der Belohnungsantizipation mit dem Faktor Apathie die Idee, dass den beiden Negativsymptomfaktoren unterschiedliche neurobiologische Mechanismen zugrunde liegen.

In der zweiten Studie (Kapitel 2.2 & Appendix B) untersuchen wir eine tonische Form der Belohnungsantizipation, das heisst, wie der Ausblick eine Belohnung zu erhalten ein Verhalten über eine längeren Zeitraum moduliert. Wir waren spezifisch daran interessiert, wie Anreize die kognitive Leistung verändern, da die Akquirierung der meisten Belohnungen im Alltag vom Einsatz kognitiver Bemühungen abhängen. Obwohl Negativsymptome mit Defiziten in der Belohnungsantizipation und der Kognition in Verbindung gebracht wurden, hat keine Studie je die neurobiologische Basis der Interaktion zwischen diesen beiden Domänen untersucht. Wir verwendeten eine bekannte Arbeitsgedächtnisaufgabe und variierten die Belohnung für die Leistung. Neben anderen Regionen fanden wir Aktivität im rostralen anterioren Cingulum, welches als Drehkreuzregion betrachtet wird, die Motivation und Kognition miteinander verbindet und die Nachfrage nach Ressourcen reguliert. Wir fanden keine signifikanten Gruppenunterschiede zwischen Patienten und gesunden Kontrollen, was indiziert, dass sich diese beiden Gruppen nicht darin unterscheiden, wie sie Belohnungsinformation zu integrieren und wie sie diese dazu nutzen, die kognitive Leistungsfähigkeit zu steigern. Wir haben jedoch entdeckt, dass die Aktivität im anterioren Cingulum negativ mit dem Negativfaktor reduzierter Ausdruck korreliert. Dies ist grundsätzlich in Übereinstimmung mit der Theorie der limitierten kognitive Ressourcen von Cohen (2012). Allerdings erweitern wir das Modell Cohens indem wir vorschlagen, dass reduzierter Ausdruck nicht bloss durch limitierte kognitive Ressourcen entsteht, sondern auch durch eine inadäquate Modulation der verfügbaren Ressourcen. Zudem liefern wir als erste Gruppe ein mögliches neurobiologisches Modell des reduzierten Ausdrucks.

In der dritten Studie (Kapitel 2.3 & Appendix C) untersuchen wir ob Patienten mit einer Schizophrenie Defizite in der Belohnungsrepräsentation haben. Da die meisten Belohnungsrepräsentationen nicht angeboren sind, müssen sie zuerst gelernt werden. Deshalb kann man die Repräsentation von Belohnungen als Ergebnis eines Lernprozesses betrachtet werden. Ein wesentlicher Mechanismus der Encodierung von Belohnungen ist die kontextspezifische Adaptation der neuronalen Sensitivität. Um eine theoretisch unlimitierte

Menge an Belohnungen mit einer limitierten Menge an Neuronen zu encodieren, passen die Neurone ihre Feuerungssensitivität den momentan verfügbaren Belohnungen in der Umgebung an. Dies garantiert, dass belohnungssensitive Neurone immer die ganze Bandbreite ihrer möglichen Feuerungsrate ausnutzen, was eine optimale Diskriminierung zwischen verschiedenen Belohnungsstufen ermöglicht. Obwohl verschiedenste Studien bereits angedeutet haben, dass Defizite in der Belohnungsrepräsentation mit ein Grund für Defizite im Verstärkungslernen, der Kosten-Nuten-Berechnung oder Defizite im assoziativen Lernen sein könnten, hat noch keine Studie je das adaptive Codieren von Belohnungen untersucht. Wir zeigen zum ersten Mal, dass Patienten mit einer Schizophrenie solche Defizite aufweisen, was dafür spricht, dass sie Belohnungen unpräzise repräsentieren. Wir glauben, dass dieses Defizit die Grundlage für viele dysfunktionale Belohnungs-verarbeitungsprozesse darstellen könnte, da eine akkurate Repräsentation eine wichtig Voraussetzung für alle Prozesse der Belohnungsverarbeitung ist. Zudem liefern wir Beweise, dass dieses Defizit mit der generellen Symptomschwere zusammenhängt, was nahelegt, dass es sich bei diesem Defizit um eine basale Dysfunktion der Schizophrenie handeln könnte.

Zusammenfassend habe wir Beweise dafür gefunden, dass spezifische Prozesse der Belohnungsverarbeitung, wie die phasische und tonische Belohnungsantizipation und das adaptive Codieren von Belohnungsinformation, mit den Symptomen der Schizophrenie zusammenhängen. Das zeigt, dass Abnormitäten in spezifischen Belohnungsverarbeitungs-prozessen, welche alle durch Dopamin beeinflusst werden, das Potential haben, Erkenntnisse über die Symptomatik und die zugrundeliegenden neurobiologischen Mechanismen zu liefern. Dies nährt die Hoffnung auf spezifischere und effizientere Behandlungen. Die Resultate dieser Dissertation unterstützen auch die gestiegenen Bemühungen, Defizite in der Belohnungsverarbeitung als transdiagnostischen Rahmen für die Untersuchung von motivationalen Einschränkungen und Lerndefiziten in anderen psychiatrischen Erkrankungen, wie zum Beispiel der unipolaren und bipolaren Depression, zu nutzen.

1. Introduction

1.1. Schizophrenia and its symptoms

Schizophrenia is one of the most debilitating mental disorders, severely impairing individuals' social and occupational functioning as well as quality of life (Mueser & McGurk, 2004; S. K. Schultz & Andreasen, 1999). The prevalence of schizophrenia is about 1% across cultures, with men being slightly more affected than women (1.4:1) (Aleman, Kahn, & Selten, 2003; McGrath, Saha, Chant, & Welham, 2008). Furthermore, men tend to have an onset between the ages of 15 to 25, whereas women tend to have an age of onset between 25 and 35. This is proposed as one of the factors that contributes to a more severe disease course in men compared to women, since the later onset in women is associated with a better social development and functioning before the start of the illness (Angermeyer, Kühn, & Goldstein, 1990; Häfner, 2000). Besides affecting mental health, patients with schizophrenia die 12 – 15 years before the average population, thereby causing more loss of lives than most cancers and physical illnesses (Saha, Chant, & McGrath, 2007).

The term schizophrenia does not refer to a single disease with a specific course, but rather to a complex disease spectrum with diverse clinical presentations and treatment responses across individuals (Heckers et al., 2013; Tandon et al., 2013). Symptoms characterizing schizophrenia can be grouped into five symptom domains: 1) hallucinations, 2) delusions, 3) disorganized thought (speech), 4) disorganized or abnormal motor behavior (including catatonia), and 5) negative symptoms (Heckers et al., 2013; van Os & Kapur, 2009). According to the DSM-5 diagnostic criteria, at least one positive symptom (delusions, hallucinations, disorganized thoughts), and a total of at least two symptoms have to be present for a significant portion of time during a one-month period within a total duration of illness of six month (APA, 2013). Furthermore, a substantial deterioration of social and occupational functioning is required to fulfill the diagnostic criteria of schizophrenia. Apart of these classical psychopathological domains that are based on a categorical assessment of schizophrenia, models with an underlying dimensional structure have been proposed (Heckers et al., 2013; van Os & Kapur, 2009). Analyses of the psychopathological features revealed that symptoms can be grouped into five dimensions: a positive-symptom dimension (including delusions, hallucinations, disorganized thoughts), a negative-symptom dimension (including avolition, anhedonia, social withdrawal, blunted affect and alogia), a cognitive-symptom dimension (reflecting alterations in neurocognition such as attention deficits, impairments in memory and executive functioning), and two affective dimensions, i.e., depressive symptoms and manic symptoms (see Figure 1) (van Os & Kapur, 2009). Importantly, dimensional approaches are proposed to be more useful at predicting clinical course and treatment needs in comparison to traditional categorical diagnostic criteria (Allardyce, Gaebel, Zielasek, & van Os, 2007).

In the last decades, much effort has been invested to elucidate the underlying pathophysiology of distinct subdomains of these symptom dimensions. A lot of research has especially focused on the structure of negative symptoms since treatment responsiveness of current pharmacological therapies is negligible (Erhart, Marder, & Carpenter, 2006). There is now consensus that the five negative symptoms avolition, anhedonia, social withdrawal, blunted affect and alogia can be group into two factors: 1) apathy, consisting of avolition, anhedonia, as well as social withdrawal, and 2) diminished expression, consisting of blunted affect and alogia (Blanchard & Cohen, 2006; Foussias & Remington, 2010; Messinger et al., 2011; Strauss et al., 2012).

The current understanding of the etiology of schizophrenia is a multifactorial model that unites various factors, such as genetics, neurodevelopment, and environment. With regard to neurochemical abnormalities, the dopamine circuitry has been postulated as primary pathology for more than 50 years (Carlsson & Lindqvist, 1963; van Rossum, 1966). The theory posits that positive and negative symptoms are – among other factors – the result of a dysbalanced dopamine release in cortical and subcortical regions. Whereas positive symptoms are attributed to an excess of dopamine in the mesolimbic system (resulting in the attribution of aberrant salience to irrelevant stimuli), negative symptoms are linked to a hypodopaminergic function in the mesocortical system (which leads to a failure in appropriately responding to meaningful reward cues) (Kapur, 2003).

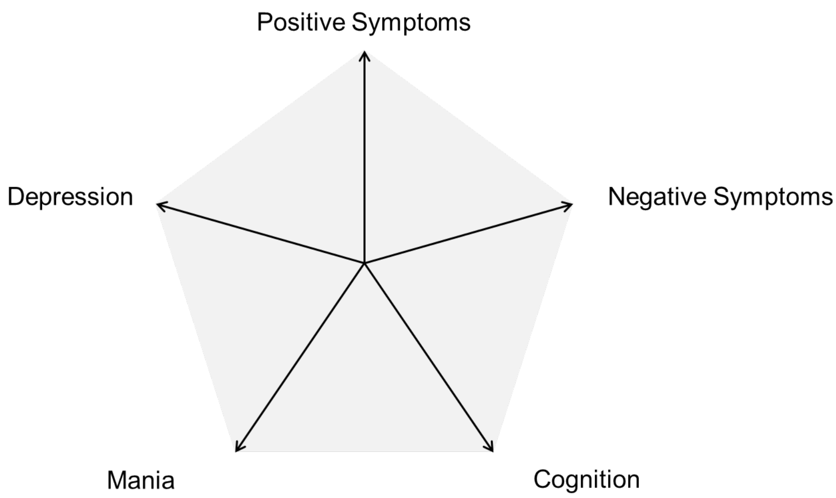

Figure 1. Symptom dimensions of schizophrenia (adapted from van Os & Kapur, 2009)

1.2. Reward processing

Rewards are crucial for survival and reproduction. Ultimately, they are responsible that organisms engage in their most basic behaviors: eating, drinking, and mating. The impacts of rewards range from the control of vegetative states to the organization of goal-directed behavior (McClure, York, & Montague, 2004; W. Schultz, 2000; Wolfram Schultz, 2015). According to Wolfram Schultz (2015), the acquisition of reward is so critical for survival and procreation that rewards might even be the reason why brains evolved in multicellular organisms. Because reward acquisition is so essential, organisms able to acquire more of them have an evolutionary advantage. Hence, throughout evolution, brains were optimized to process rewards by enabling organisms to learn about them, to identify and seek them, and to acquire them through decisions and actions.

The evolutionary importance of reward processing stimulated great research interest. However, since our brain is not equipped with specific reward receptors, we cannot investigate reward processing by simply looking at specific properties of such receptors. We see, feel, taste and smell rewarding stimuli with the same sensory systems as non-rewarding stimuli. Furthermore, rewards do not carry special physical properties, which makes it impossible to recognize them via specific markers. Instead, what makes rewards unique is the behavioral reaction they elicit. Therefore, behavioral theories that provide concepts of reward functions are crucial for investigating reward processing (Berridge & Robinson, 2003; Berridge, Robinson, & Aldridge, 2009; W. Schultz, 2000; Wolfram Schultz, 2015). Currently, three major, closely interwoven reward functions (with further subdivisions and levels) are propagated (Berridge et al., 2009; Wolfram Schultz, 2015):

1. liking/positive emotions[*]

   Rewards can elicit positive emotions, above all, the experience of pleasure.

2. wanting/approach behavior[*]

   Rewards serve as motivational magnets, they attract us, lead to approach behavior and let us invest additional effort.

3. learning

   Rewards may elicit a learning process. We associate and predict rewards based on past experience. Learning can be implicit or explicit and the products of learning can be declarative or procedural.

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[*] „liking“ and „pleasure“ as well as „wanting“ and „approach behavior“ are used interchangeably here.

Although there are no specific reward receptors, evidence supports the notion that partly dissociable brain circuits are particularly sensitive to reward and mediate the three different functions of reward. However, the identification of separate brain substrates remains a major challenge since rewarding stimuli elicit many or all of these reward components simultaneously and hence, activate all involved brain regions at the same time (Berridge & Kringelbach, 2008). That the brain circuits involved in the functions of liking, wanting, and learning are interconnected is also a necessity since these three functions need to interact in order to serve their ultimate purpose: survival and procreation. However, for a better understanding of reward processing it is important to tease apart the activity induced by a reward and relate it to the according functions.

Particularly liking has been associated with a separable brain circuit compared to wanting and learning. It is assumed that the opioid, cannabinoid and GABA-benzodiazepine neurotransmitter systems is involved in the experience of pleasure. 'Hedonic hotspots' in the limbic system, specifically in the shell of the nucleus accumbens and the ventral tegmentum have been found to enhance pleasure reactions (Kringelbach & Berridge, 2009). Wanting and learning on the other hand are mainly associated with the dopaminergic system. However, the differentiation of these two reward components is less clear. Both functions have been associated with activity in mesocorticolimbic and mesostriatal dopamine neurons, including their widespread projections to cortical and subcortical structures, such as the striatum, the anterior cingulate, the insula and the prefrontal cortex (Berridge et al., 2009; W. Schultz, 2000; Wolfram Schultz, 2013; Ziauddeen & Murray, 2010).

Major functions of reward	Liking/ Positive emotions	Wanting/ Approach behavior	Learning
Psychological components	Subjective or objective hedonic component of reward; reflects the ability to enjoy a stimulus/event	Stimuli associated with hedonic impact are usually attractive; they elicit approach behavior and let us invest additional effort	Learning produces links between stimuli or the consequences of actions; associations, representations and predictions about reward require learning

Figure 2. Major functions of rewards and their psychological components (adapted from Berridge et al., 2009 and Wolfram Schultz, 2015)

1.3. Reward processing deficits in schizophrenia

With the proposition of sophisticated behavioral theories of reward functions and their underlying neurobiological substrates, evidence of reward processing abnormalities in patients with schizophrenia accumulated. Positive symptoms have been found to correlate with dysfunctional learning mechanisms, and negative symptoms have been associated with deficits in all three components of reward.

Early studies proposed the very intuitive theory that negative symptoms originate from diminished hedonic responses. It was thought that patients do not engage in goal-directed behavior because they simply do not experience pleasure when they perform such activities. Additionally, a numbing or lack of hedonic experience would also help to explain diminished expressive behavior and flattened affect. However, accumulated evidence suggests that this is not the case: patients with schizophrenia report similar levels of positive emotions and show comparable brain activity to healthy controls when confronted with an emotionally evocative stimulus. Hence, a lack in the experience of positive emotions cannot explain why patients with schizophrenia show reduced goal-directed behavior and diminished expression (Berridge & Kringelbach, 2008; Gold, Waltz, Prentice, Morris, & Heerey, 2008; Strauss, Waltz, & Gold, 2013).

Another possibility that could explain the emergence of negative symptoms despite intact hedonic responses is a deficit in wanting. Although one might think that liking and approach behavior are related or even identical, i.e., most rewards that are liked are also approached, these two reward functions are in fact dissociable on a psychological and neurobiological level (see chapter 1.1 & 1.2). Therefore, although a stimulus might evoke positive emotions when encountered or consumed, it does not necessarily induce approach behavior in the future. Hence, an explanation for the reduced goal directed behavior could be a diminished wanting of a reward: a patient might like a reward, but he might not feel attracted to it and hence, won't approach it. In very severe cases, this deficit could explain apathetic behavior, as presented in patients with schizophrenia (Strauss et al., 2013). Various studies have investigated approach behavior in schizophrenia with the monetary incentive delay (MID) task developed by Knutson, Fong, Adams, Varner, & Hommer (2001). The task is based on an instrumental conditioning task applied in animal studies and allows elucidating different stages of reward processing, in particular reward anticipation, which is one important component of wanting (Arias-Carrión & Pŏppel, 2007; B. Knutson, Fong, et al., 2001; Brian Knutson & Heinz, 2015; Wolfram Schultz, 2015). The MID task consists of various trials that start with the announcement of a (variable) incentive – symbolized by a cue – which is linked (with a certain contingency) to the receipt of this incentive. To receive the financial incentive, participants have to correctly react to a target stimulus, which is presented after the reward-inducing cue. On the neural level, there is consistent evidence that the ventral striatum (VS) plays a crucial role in anticipating rewards (B. Knutson, Adams, Fong, & Hommer, 2001; Sescousse, Caldú, Segura, & Dreher, 2013). Several research groups reported that patients with schizophrenia show diminished VS activity during reward anticipation (Grimm et al., 2014; Juckel et al., 2006; R. W. Morris et al., 2012; Nielsen et al., 2012; Schlagenhauf et al., 2008; Simon et al., 2010). Additionally, a few studies linked this (hypo-)activation of the VS to negative symptoms, or the factor apathy (Simon et al., 2010; Waltz et al., 2010). However, no clear distinction between neurobiological correlates of the two negative symptom dimensions apathy and diminished expression has been shown. A specific correlation of reward anticipation deficits (as expressed in a reduced VS activation) with apathy would not only support the theory of a two factor solution of negative symptoms, but also offer insight into the underlying behavioral mechanism and neurobiology of apathy.

Whereas the MID task allows investigating short term, phasic effects of reward anticipation, many real life situations require the maintenance of reward information for longer periods of time. Additionally, the required action to obtain the reward is often complex and involves the investment of cognitive effort. Hence, the acquisition of rewards in everyday life requires a translation of reward information into goal representations and a modulation of behavior for an extended period of time. Various studies elucidated this process in healthy controls, showing that the prospect of a reward enhances cognitive performance and leads to additional activity in sensory and cognitive areas (Beck, Locke, Savine, Jimura, & Braver, 2010; Kennerley & Wallis, 2009; Krawczyk, Gazzaley, & D'Esposito, 2007; Rowe, Eckstein, Braver, & Owen, 2008). A proposed mechanism that leads to a better performance when a reward is at stake is the prioritization of the process required to obtain the reward. This idea is based on the notion that our brain has limited perceptual capacities. Stimuli within our environment are constantly competing for perceptual resources and control of behavior. High rewards are treated with priority and receive additional resources that are either activated or reallocated (Pessoa, 2009). On the neural level, the anterior cingulate cortex is suggested to play an essential role in controlling the distribution of resources and in behavioral adaptation. It acts as a hub and links reward related structures – such as the ventral striatum – with brain structures involved in cognition – such as the lateral prefrontal cortex (Krebs, Boehler, Roberts, Song, & Woldorff, 2012; Pessoa, 2008, 2009; Pessoa & Engelmann, 2010; Vassena et al., 2014). With regard to negative symptoms in schizophrenia, there is mixed evidence of improved performance due to reward anticipation. Whereas various studies found no effect of reward on performance, others found an improvement (Barch, Pagliaccio,

& Luking, 2015). However, up to today, there are no published fMRI studies examining the interaction of reward and cognition in schizophrenia.

Besides the reported deficits in subcomponents of wanting, schizophrenia has been associated with deficits in various components of learning, e.g., negative symptoms have been linked to deficient reinforcement learning, and positive symptoms have been associated with aberrant salience coding (Corlett et al., 2007; Deserno, Boehme, Heinz, & Schlagenhauf, 2013; Gold JM, Waltz JA, Matveeva TM, & et al, 2012; R. Morris, Griffiths, Pelley, & Weickert, 2013; Murray et al., 2007, 2008; Strauss et al., 2011; Waltz & Gold, 2007). Learning is an extremely critical function since most representations of rewards as well as relationships between rewarding stimuli and actions are not inherent, and hence, have to be learned first. Furthermore, due to the changes of internal and external states, these representations and associations have to be constantly updated (Berridge et al., 2009; Wolfram Schultz, 2015). An accurate representation of reward is crucial and can be seen as a prerequisite to choose the optimal action (Tobler, Fiorillo, & Schultz, 2005). A major challenge in reward representation is the theoretically unlimited number of rewards that have to be encoded by a limited number of reward sensitive neurons. Recent evidence suggests that the brain solves this problem by adjusting the neural sensitivity to the currently available rewards, a mechanism called adaptive coding of rewards (Cox & Kable, 2014; Kobayashi, Carvalho, & Schultz, 2010; Park et al., 2012; Tobler et al., 2005). This adaptation is necessary to ensure optimal discriminability of rewards. Hence, a failure in this adaptation leads to imprecise representations, which could potentially affect all reward-related processes and result in detrimental decision-making. Although it has been suggested that patients with schizophrenia have a compromised ability to represent rewards, no study has ever elucidated dynamic neural representation of rewards in schizophrenia (Gold JM et al., 2012; Gold et al., 2008).

1.4. Research objectives

The aim of this dissertation is to fill the research gaps mentioned in chapter 1.3 and to further elucidate reward processing deficits and their relation to distinct symptoms in schizophrenia. The focus of study 1 and study 2 was to elucidate deficits regarding motivational aspects of reward and their relation to negative symptoms. Study 3 was implemented to investigate deficits in reward learning and their link to the symptomatology in general (see Figure 3).

The aim of study 1 was very specific: clarifying the relation of the two negative symptoms factors apathy and diminished expression with regard to the anticipation of reward. In contrast to most studies elucidating reward anticipation, we applied a modified version of the MID task where rewards are not probabilistic, but dependent on individual performance. We believe that this version better operationalizes goal-directed behavior and is therefore better aimed to elucidate the relation with the factor apathy. Our hypothesis for study 1 was that the activity in the ventral striatum during reward anticipation was specifically correlated with apathy, but not with diminished expression.

In study 2, we investigated another component of wanting. Compared to study 1, we elucidated tonic reward anticipation effects and their impact on cognitive performance. We were interested whether patients with schizophrenia are able to translate reward information into goal representations, maintain this information for an extended period of time and modulate their behavior accordingly. Importantly, we wanted to specifically elucidate the effects of anticipated rewards on cognitive performance since the acquisition of rewards in everyday life is mainly achieved through cognitive effort. We applied a well-known working memory task and varied the incentive for performance. We chose to model the task with a block design because it allows a better investigation of tonic reward effects, since participants need to maintain the reward information for a longer period of time. We hypothesized that patients with schizophrenia would not profit as much as healthy controls from a modulation of cognitive performance with reward. Furthermore, we thought the modulation would be correlated with negative symptom severity. On the neural level, we expected that patients would show lower ACC activity and a correlation of that activity with negative symptoms.

In study 3 we aimed to investigate the neural representations of rewards. Recent evidence suggests that these representations are context specific and adjust to the currently available rewards in the environment. Although some studies reported that reward representations are deficient in schizophrenia, no study ever elucidated adaptive coding of reward in schizophrenia. To analyze adaptive reward coding, we focused the analysis of the MID task on the outcome phase under two different reward contexts. We hypothesized that patients with schizophrenia show deficits in adaptive reward coding and assumed that these deficits are related to the symptomatology.

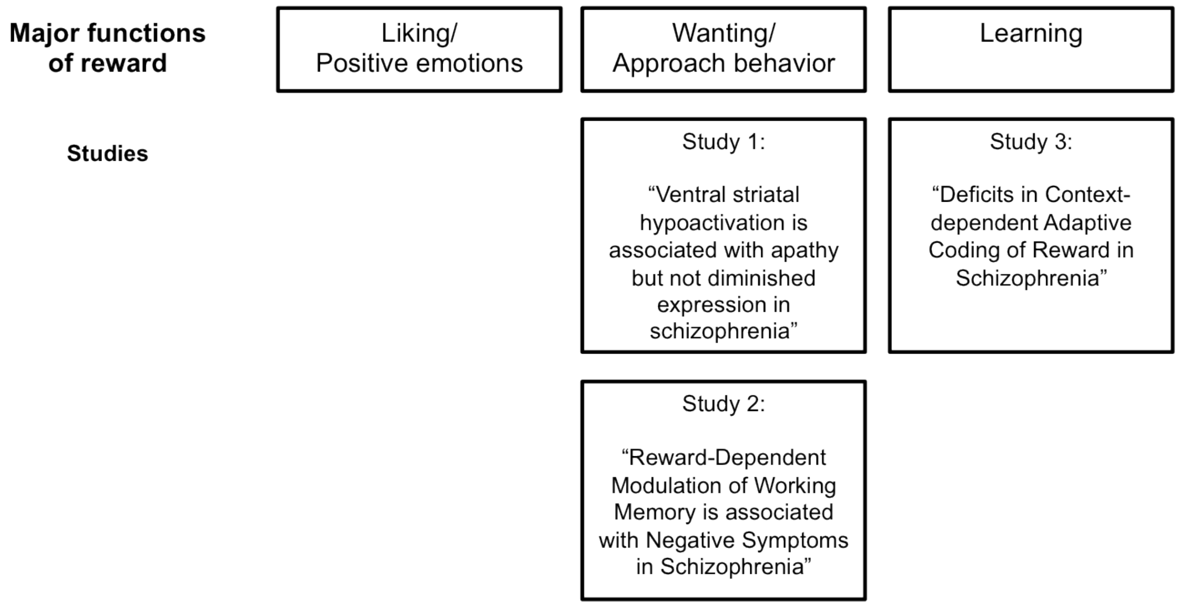

Figure 3. Overview of the conducted studies and their relation to the major functions of reward.

2. Summary and Discussion of Studies

2.1. Study 1: Ventral striatal hypoactivation is associated with apathy but not diminished expression in schizophrenia[1]

Previous studies have shown that patients with schizophrenia and their relatives show reduced activation in the ventral striatum during reward anticipation, although there are also reports where no significant differences were found, particularly in patients treated with atypical neuroleptics (Grimm et al., 2014; Juckel et al., 2006; Leeuw, Kahn, & Vink, 2015; Nielsen et al., 2012; Schlagenhauf et al., 2008; Simon et al., 2010). Additionally, some studies reported a correlation of (blunted) striatal activity with negative symptoms, or apathy (Simon et al., 2010; Waltz et al., 2010). However, no study has yet provided results that this association is specific to the factor apathy, and not related to the factor diminished expression. The aim of our study was to clarify the exact nature of this association. Our hypothesis was that the ventral striatal (hypo-)activation during reward anticipation was specifically related to apathy, and not to diminished expression.

We recruited 27 patients with schizophrenia and 25 healthy controls who all performed a variant of the monetary incentive delay task (MID) during event-related fMRI. The MID task allows investigating various reward components, among others, reward anticipation. Each trial starts with the presentation of a cue that indicates a certain reward context, followed by a delay of 2 – 3 seconds (= reward anticipation phase). We included three different cues, indicating three different contexts: a neutral context, a low reward context and a high reward context. Subsequent to the presentation of the cue and the delay, participants have to react to a target stimulus. Out of three symbols in a row, they need to identify an outlier (which was either the symbol on the left or on the right side) and press the according response button. In case of a correct answer to the target stimulus, participants receive a reward for their performance. In contrary to the original version of the MID developed by B. Knutson, Fong, et al. (2001), reward outcome in our version was not determined probabilistically, but directly influenced by individual performance. The rationale behind a direct link of performance and outcome was that it better simulates goal-directed behavior, since outcome was completely determined by behavior. Additionally, this modification also enabled us to study adaptive coding of reward (see chapter 2.3). Furthermore, our MID task contained an algorithm that calculated the performance on basis of the last 15 response times of the previous 15 correct trials. This modulation should account for individual differences in response time and thus lead to constant rewards in all subjects. Importantly, all subjects performed 2 practice sessions before the actual experimental session started. The first practice session was performed outside the MRI scanner and was meant to familiarize the participants with the

[1] Please see appendix A for full-length research paper

task and served to measure the range of individual response times. For the second practice session inside the MRI scanner, the subject specific response times were used to calculate performance. During this practice session, subjects could get used to the new environment and the response box while the task has already adapted to the individual response times.

Analyzing the behavioral data, we found a significant main effect of reward regarding response time. More specifically, we found that participants were significantly faster with increasing reward levels, a phenomenon called reward-related speeding. There was no group difference regarding response time and we found no correlation of reward-related speeding and negative symptoms. On the neural level, we found that patients and healthy controls activated the ventral striatum stonger when anticipating a reward compared to when anticipating no reward. We did not find a significant difference in ventral striatal activation between groups. This result is in line with results reported by Juckel et al., (2006), Schlagenhauf et al. (2008), and Simon et al. (2010), who also found no significant difference between patients treated with atypical neuroleptics and healthy controls. Our correlation analyses however showed that the activity in the VS was significantly and specifically correlated with apathy, but not with diminished expression. The two significantly different correlations provide evidence of a specific association of VS activation and apathy. To our knowledge, this is the first study showing this specific association, which provides strong support for the idea of different underlying neural correlates of apathy and diminished expression. Furthermore, these results provide a link for a pathophysiological mechanism of apathy. We argue that reduced activation in the VS reflects a reduction in wanting of potential rewards. If a person cannot be motivated to achieve a certain reward in the future, he will not engage in goal-directed behavior, which can – in extreme cases – lead to apathetic behavior as seen in patients with negative symptoms. The strong link between apathy and reduced VS activity might also explain the mixed findings of group differences in VS activation, meaning that it depends on the level of apathy in the patient group whether a group difference becomes significant or not.

In sum, we present results showing that ventral striatal activity during reward anticipation is inversely correlated with apathy, but not with diminished expression. We are the first group to report a differentiation of the two negative symptoms factors on a neurobiological level. The implication of this intriguing finding is twofold: First, we argue that hypoactivation in the ventral striatum specifically reflects reduced wanting of a reward, which leads to a reduction of goal-directed behavior and the expression of apathetic behavior in patients with schizophrenia. Second, the specific correlation of ventral striatal activity during reward anticipation with apathy supports the notion that the two negative symptom factors have specific underlying neurobiological mechanisms. This evidence of a differentiation of the two factors highlights the importance of assessing both factors carefully and targeting treatment for both factors separately.

2.2. Study 2: Reward-Dependent Modulation of Working Memory is associated with Negative Symptoms in Schizophrenia[2]

Research on dysfunctions in reward processing and cognition has long been conducted separately (Braver et al., 2014; Pessoa, 2009). Likewise, deficits in these domains have been related to separate, functionally specialized brain regions (Pessoa, 2008). While reward processing has been linked to mainly dopaminergic midbrain regions, such as the ventral striatum, cognitive processing deficits have been associated with aberrant activity in primarily prefrontal regions (Barch & Ceaser, 2012; Juckel et al., 2006; Manoach, 2003; Nielsen et al., 2012; Schlagenhauf et al., 2008; Simon et al., 2010; Waltz et al., 2010). However, recent work suggests a strong interaction between cognition and reward. In line with this notion, various studies have shown that the prospect of a reward promotes performance in multiple task domains and leads to the modulation of cognitive brain regions (Chiew & Braver, 2011; Krebs et al., 2012; Locke & Braver, 2008). It is thought that the outlook of a reward prioritizes processes that lead to the harvest of the potential reward by the assignment of additional resources or by withdrawing resources from other concurrent processes. The ACC has been suggested to play a pivotal role in this process by acting as a hub, thereby linking cognitive and affective brain regions. It is theorized that the ACC is engaged by reward-related regions such as the VS and OFC and further influences prefrontal regions associated with cognition and cognitive control (Pessoa, 2009; Vassena et al., 2014).

The aim of this explorative study was to elucidate whether negative symptoms reflect problems in using reward information to increase cognitive performance. Our hypothesis was that patients with schizophrenia would not profit as much from a reward enhancement effect as healthy controls. Furthermore, we expected that impairments in reward modulation are correlated with negative symptom severity. On the neural level, we hypothesized that enhanced activity in the ACC and other working memory related regions induced by the reward-cognition interaction was significantly lower in the patient group compared to the healthy control group. Additionally, our hypothesis was that this attenuated effect correlated with negative symptoms.

[2] Please see appendix B for full-length research paper

To operationalize an interaction of reward and cognition, we applied a letter variant of the n-back working memory task and varied the incentive for performance. We manipulated cognitive load (0-back vs. 2-back) and the amount of reward (no reward/reward) for performance, which resulted in a total of 4 different conditions. In the 0-back condition, participants were required to press a button whenever the letter “x” appeared on the screen. In the 2-back condition, participants had to press a button, whenever the letter they saw was equal to the letter presented before the last one. Each trial consisted of twelve letters and contained 4 target stimuli (hits). At the beginning of a trial, participants were informed about the cognitive load (0-back/2-back) and the level of reward (reward/no reward) of the upcoming trial. At the end of each trial, after participants performed the working memory task, they received feedback about their performance, which was measured as the standardized probability of a hit minus the standardized probability of a false alarm, also called sensitivity index d’. Additionally, we measured response time, i.e., the time to respond after the presentation of a hit. The amount of reward they won – in case of a rewarded trial – depended directly on their performance, i.e., on the sensitivity index d’.

With regard to performance (= sensitivity index d’), we did not find a significant difference between both groups. However, across all subjects, we found a significant main effect of cognition, meaning that participants performed significantly better in the 0-back condition relative to the 2-back condition. We did not find any significant effect of reward or any significant interaction effect on accuracy. Likewise, we did not find any significant correlation of negative symptoms and sensitivity. Regarding response time, we found a main effect of group, indicating that the healthy control group responded significantly faster than the patient group across conditions. Across groups, we also found a main effect of cognition, showing that participants were faster in the condition with low cognitive load, and a main effect of reward, implicating that participants responded faster in case of a rewarded trial. However, we did not find any interaction effect. Regarding associations of response time and negative symptoms, we found a significant correlation of apathy with the factor cognitive load and the reward-cognition interaction ((2-back/reward – 0-back/reward) – (2-back/no reward – 0back/no reward)), indicating that cognitive load and the integration of complex information reduces response time in patients with apathy.

Regarding the imaging data, we focused our analyses on the reward-cognition interaction contrast ((2-back/reward – 0-back/reward) – (2-back/no reward – 0back/no reward)) and restricted our search volume, based on our a priori hypothesis, to the frontal cortex (including ACC). Pooling over all subjects, we found significant activation in the bilateral and medial superior frontal gyrus and the right rostral anterior cingulate. This finding is in line with our a priori hypothesis: Because the successful completion of the working memory task led to a financial reward, the respective process was prioritized and additional cognitive resources were recruited in order to maximize performance. The proposed mechanism is that the ACC exerts its influences to control resource demands via interconnections with cortical areas, such as the (pre-)motor cortex and the lateral prefrontal cortex, which might explain the significant activation in these regions. In sum, we found 4 clusters that were significantly more active when working memory performance (2-back vs. 0-back) was rewarded, compared to when it was not rewarded, suggesting a role of these regions in integrating reward information and cognition. When comparing the groups, we did not find any significant differences between the healthy control group and the patient group, implying an intact neural mechanism in schizophrenia. However, within the patient group, we found that activity in the ACC was significantly and specifically correlated with the factor diminished expression, indicating that patients with more severe diminished expression symptoms have difficulties in (up-)regulating their processing resources in order to meet the current resource demand. This finding is in line with the cognitive resource limitations model of diminished expression proposed by Cohen et al. (2014; 2012). This model is based on the fact that expressive behavior requires a range of mental resources. During a social interaction for example, individuals must track and update the conversation, integrate and hold important information, observe the implicit and explicit behavior of the conversational partner, and so forth. The cognitive resource limitations model suggests that diminished expression result from a lack of available resources. Our data extends this theory by suggesting that patients with more diminished expression do not solely have less cognitive resources, but experience difficulties in adjusting their resources according to priority, which results in diminished expressivity.

To summarize, in study 2, we investigated the effects of prospective rewards on working memory performance in patients with schizophrenia and healthy controls. We found that anticipating a reward in a cognitively effortful task leads to an additional activation of the rostral anterior cingulate (ACC) and the lateral prefrontal cortex in both groups. This finding is in line with previous research demonstrating that rewards lead to enhanced brain activity in task-related regions, regions involved in executive control, and so-called hub regions, like the ACC. We did not find any significant group difference in the reward-cognition interaction on the behavioral and neural level. This indicates that patients with schizophrenia are able to integrate information about prospective rewards and utilize this information in order to increase their performance. However, within the patient group, we found that the enhanced ACC activity in the rewarded vs. non-reward working memory contrast was inversely correlated with the negative symptom factor diminished expression. This finding is generally in line with the cognitive resource limitation model proposed by Cohen (2012), which proposes that – based on the fact that expressive behavior requires a range of mental resources – diminished expression originates from a lack of available cognitive resources. We expand this model by arguing that patients with diminished expression not only have less cognitive resources available, but that they are not able to recruit sufficient cognitive resources to meet the required demands of rewarded tasks and hence, show diminished expression. Furthermore, we are the first group to propose a potential neurobiological mechanism of diminished expression.

2.3. Study 3: Deficits in Context-dependent Adaptive Coding of Reward in Schizophrenia[3]

Schizophrenia has been associated with various reward processing abnormalities. It is thought that these deficient processes are – besides or instead of primary cognitive impairments – jointly responsible for several critical cognitive and affective deficits. While negative symptoms have been linked to reward anticipation deficits (see chapter 2.1 & 2.2), impaired reinforcement learning (RL) and aberrant cost-benefit computations, positive symptoms have been implicated with the aberrant coding of salience (for review see Barch et al., 2015; Gold et al., 2008; Strauss et al., 2013). A commonality of all these deficient processes is the requirement of a precise representation of reward. In order to precisely encode a potentially infinite quantity of rewards with only a limited number of reward coding neurons, neurons adjust their coding range to the current (reward) context (Tobler et al., 2005). With this efficient allocation of resources, neurons can exploit their entire dynamic range within any given context, thereby guaranteeing optimal sensitivity and discriminability between different rewards. The aim of our study was to elucidate whether potential deficits in context-dependent adaptive coding could reflect a basic dysfunction of reward processing in schizophrenia and whether there is a correlation of the degree of adaptive coding with symptomatology.

To elucidate the adaptation of neural sensitivity to the currently available rewards, we analyzed the data of the MID task of the sample described in chapter 2.1. However, in contrary to study 1, we focused our analyses on the reward outcome phase and not on the reward anticipation phase, which reflects reward representation as compared to reward anticipation. As outlined in chapter 2.1, a cue at the beginning of each trial determines the current reward context. Our version of the task consisted of three different cues, indicating

[3] Please see appendix C for full-length research paper

three different reward contexts: a no reward context, a low reward context, and a high reward context. In the low reward context, participants could win between CHF 0 and CHF 0.4, in the high reward context, they could win between CHF 0 and CHF 2. Due to the different reward range in the low and high reward context, it is possible to investigate adaptation of neural sensitivity to rewards. According to the efficient coding hypothesis, the slope of the neural response function should be steeper with a smaller reward range compared to a larger reward range because neurons always adapt to the currently available rewards to exploit their entire dynamic firing range. Hence, in order to test for adaptive coding, we tested the slope difference of the neural response functions of both reward contexts and compared both groups for significant differences. Furthermore, we tested whether there is an association of the degree of adaptive coding with psychopathological ratings.

Regarding response time, we found a significant main effect of reward, showing that participants responded faster in the high reward context compared to the low reward context (see also chapter 2.1). This finding indicates that participants adapted their behavior to the current context. Within the patient group, we did not find any significant correlation of reaction time and symptom severity. On the neural level, we found two reward coding regions in our patient group that did not show adaptive coding compared to healthy controls: the right caudate and the right anterior insula/inferior frontal gyrus. More specifically, our analysis implies that within these two regions, healthy controls – in comparison to patients with schizophrenia – show a significantly steeper slope of the neural response function in the low reward context compared to the high reward context. This finding provides strong evidence for efficient neural adaptation in healthy controls, but not in the patient group. By further analyzing the neural response functions of the patient group, we found that particularly in the low reward context, the slopes of neural response functions were very flat, only exploiting a fraction of the potential response range. Flat response functions make discriminability between different reward amounts extremely challenging and hence, lead to imprecise representations of reward information. Since an accurate representation of reward is a prerequisite for any functional reward-related process, imprecisions in the representation could contribute to a wide range of deficient reward processes in schizophrenia. Regarding reinforcement learning deficits, Strauss et al. (2011) and Gold et al. (2012) report findings that are in line with this theory by suggesting that reinforcement learning deficits are caused by difficulties in representing the relative value of response alternatives. In a study published in 2013, Gold et al. further argue that this deficit could contribute to abnormalities in effort-based decision making. They argue that it is difficult to perform accurate cost-benefit computations if the benefits are not represented precisely. The imprecise representation of reward information could also be involved in the aberrant assignment of salience, which is proposed as a mechanism for delusions (Kapur, 2003).

Furthermore, we found that the degree of the adaptive coding deficit is related to the general symptomatology of patients with schizophrenia, suggesting that this is a basic dysfunction instead of a specific neural correlate of positive, negative or depressive symptoms. This theory is supported by the fact that adaptive coding deficits could be responsible for aberrant reward-related processes associated with positive and negative symptoms. Another aspect that supports the notion of a general deficit is that context-dependent adaptation is ubiquitous and not only found in reward coding, but as well in sensory processing, which is also deficient in schizophrenia. Additionally, various studies suggested that the core deficit in schizophrenia is an accurate processing of contextual information, which is in line with the theory of a general information processing deficit (Hemsley, 2005).

In sum, we are introducing a new concept in schizophrenia research: the contextual adaptation of neural sensitivity to the current reward context. We show for the first time that patients with schizophrenia have deficits in adaptive coding of reward. A deficit in the adaptation to the current reward context leads to a diminished discriminability of rewards and causes an imprecise representation of reward information. Such an imprecise representation might have far-reaching consequences and could lie at the root of many dysfunctional reward processes in schizophrenia. We believe that this deficient mechanism of context-dependent adaptation might help to explain some of the known deficits in reward-related processes in schizophrenia, such as deficits in reinforcement learning, cost-benefit decision making, and salience coding. Furthermore, we provide evidence that the degree of the adaptive coding deficit is related to the general symptom severity of patients with schizophrenia. The association with the general symptomatology, in combination with the ubiquity of this process in the brain, suggests that this deficit could reflect a more basic dysfunction in schizophrenia. This is also in line with early studies suggesting that the core deficit in schizophrenia is the processing of contextual information.

3. General Discussion

3.1. Reward processing as a unifying framework for studying schizophrenia

Although motivational impairments and learning deficits have long been recognized as crucial impairments in schizophrenia, it has only been recently that researchers and clinicians studied these symptoms within a reward processing framework. A driving force that contributed to the effort in understanding certain aspects of the symptomatology of schizophrenia as reward-related dysfunctions were the significant advancements in understanding how organism process rewards. Central to this progress was the insight that reward processing is not a unitary construct, but consistent of several components (see chapter 1.1). The proposition of sophisticated behavioral theories of reward facilitated the development of behavioral paradigms, which subsequently promoted a better understanding of the functional neuroanatomy and neurochemistry of the various reward-related processes. Research revealed evidence that different reward components rely on partially differentiable brain circuits. This discovery highlighted the critical role of dopamine in motivation and learning. Another driving force behind the effort of studying schizophrenia in the light of reward processing deficits was a better understanding of the symptomatology, in particular the idea of a dimensional model of schizophrenia. In sum, the clear role of dopamine in reward processing and the pathology of schizophrenia, in combination with the marked motivational and learning deficits in patients with schizophrenia, made the reward system an interesting framework for studying positive, negative, and cognitive symptoms (Barch, Pagliaccio, & Luking, 2015; Wolfram Schultz, 2015; Ziauddeen & Murray, 2010)

The results of this dissertation provide further evidence that reward processing serves as an excellent framework to understand certain aspects of the symptoms of schizophrenia. By elucidating different psychological components of reward, we found evidence for relations to specific as well as general symptoms. In study 1, we found that ventral striatal activity during reward anticipation is specifically related to the factor apathy. We argue that a hypoactivation of the ventral striatum during reward anticipation reflects disrupted wanting, which causes a reduction in approach behavior. In more pronounced forms, this reduction can be expressed as apathy. In study 2, we elucidated another aspect of wanting: we applied a behavioral paradigm that allowed studying whether the anticipation of reward leads to a modulation of cognitive performance. On the neural level, the ACC has been suggested to play a pivotal role in this modulation, providing a link between cognition and reward. Our results suggest that patients with schizophrenia are – in general – able to recruit additional cognitive resources when confronted with the prospect of a reward. However, we found that ACC activity is inversely related to the factor diminished expression, which implicates that diminished expressivity is caused by an inability to manipulate perceptual resources in order to meet the current demand. This finding is generally in line with the theory that diminished expressivity is caused by a lack of cognitive resources. However, we expand this theory by proposing that it is not only the lack of cognitive resources, but also the ability to modulate these resources, which contributes to diminished expression in schizophrenia. Additionally, we provide first evidence for an underlying neural mechanism of diminished expression. In study 3, we investigated deficits in reward learning, more specifically, deficits in reward representations. We could show that patients with schizophrenia do not adapt neural sensitivity to the current reward context, which leads to imprecise reward representations. This deficit could contribute to abnormalities in various reward processes in schizophrenia, since merely all reward processes require an accurate representation. Additionally, we found that this deficit is related to the general symptomatology. With regard to the ubiquity of this process, we believe that these findings provide an avenue to defining a general impairment in information processing that underlies this disorder.

In sum, we could show that abnormalities in phasic and tonic forms or reward anticipation and deficits in adaptive coding of reward can contribute to a better understanding of the symptoms and the underlying neurobiology of patients with schizophrenia. This supports the endeavor to study the pathophysiological mechanism of positive, negative, and cognitive symptoms in the light of reward processing deficits and highlights the crucial role of dopaminergic abnormalities in schizophrenia.

3.2. Clinical implications

Experimental paradigms that are based on sophisticated behavioral theories of reward processing provide an excellent approach to study the neural underpinnings of symptom dimensions in schizophrenia. In this dissertation, we present evidence that relates negative and positive symptoms to deficits in specific reward-related processes with distinct neurobiological correlates. Neural activity in these regions could therefore serve as neuroimaging markers for pharmacological or psychotherapeutic treatment trials. Furthermore, reward processing tasks could complement the psychopathological assessments conducted by the clinician, since patients' self-reports have shown to be biased (Strauss & Gold, 2012).

The proposed mechanisms for apathy (study 1) and diminished expression (study 2) could be helpful for the development of psychotherapeutic interventions. Study 1 suggests that apathy is related to a reduced anticipation of rewards. It would be interesting to see whether reward anticipation can be enhanced by applying emotion regulation strategies. If so, these strategies could be implemented in everyday life in order to promote goal-directed behavior. Study 2 provides evidence that diminished expression is not only based on limited processing capacities, but additionally, on the appropriate regulation of these processing capacities. In addition to cognitive training, patients could be taught how to optimally prioritize tasks in order to ensure sufficient capacities, thereby reducing their diminished expressivity.

Finally, with respect to the innovation of psychopharmacological interventions, our findings of deficient adaptive coding (study 3) may contribute to basic research regarding the development of novel therapeutics ameliorating these deficits.

3.3. Limitations

Certain limitations concern all three studies presented in this dissertation. Although we did not find any statistical effect of antipsychotic medication, we cannot fully exclude potential confounding effects on the symptomatology, and the dopaminergic system in general. It would therefore be critical to replicate these studies with antipsychotic naïve patients and patients with first generation antipsychotics. Also, patients in our sample had a relatively low variance in positive and depressive symptoms. This limits the ability to differentiate specific effects of these two symptoms dimensions. Furthermore, it would be important to not only include patients with a manifest disorder, but also patients with an increased risk in order to better understand the development of symptoms. Another limitation is that we only used one specific secondary reinforces to study reward processing. However, it would be crucial to include primary rewards, such as food, liquid, or erotic stimuli in order to generalize the observed deficits to all reward categories. The application of primary rewards would also facilitate the comparison with experiments based on animal models of schizophrenia and promote reward processing as a translational framework.

3.4. Conclusion

In this dissertation, we present findings that link positive and negative symptoms to alterations in normal motivational processing and reward learning. We could show that deficits in certain subcomponents of reward processing map onto partially separable neurobiological substrates in schizophrenia, which paves the way for the development of new psychological and pharmacological treatment and intervention strategies.

Furthermore, we could show that reward processing is an optimal framework for studying motivational impairments and deficient learning processes in schizophrenia. Since these deficits are also core aspects of other psychopathologies, such as major depression and bipolar disorders, a reward processing framework can be used to study impairments across diagnostic boundaries. This will allow elucidating whether there are common psychological or neurobiological mechanisms underlying reward processing abnormalities across psychopathologies, or whether there are very specific, separable mechanisms contributing to each mental disorder.

4. References

Aleman, A., Kahn, R. S., & Selten, J.-P. (2003). Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Archives of General Psychiatry*, *60*(6), 565–571. http://doi.org/10.1001/archpsyc.60.6.565

Allardyce, J., Gaebel, W., Zielasek, J., & van Os, J. (2007). Deconstructing Psychosis conference February 2006: the validity of schizophrenia and alternative approaches to the classification of psychosis. *Schizophrenia Bulletin*, *33*(4), 863–867. http://doi.org/10.1093/schbul/sbm051

Angermeyer, M. C., Kühn, L., & Goldstein, J. M. (1990). Gender and the course of schizophrenia: differences in treated outcomes. *Schizophrenia Bulletin*, *16*(2), 293–307.

APA. (2013). American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing.

Arias-Carrión, O., & Pŏppel, E. (2007). Dopamine, learning, and reward-seeking behavior. *Acta Neurobiologiae Experimentalis*, *67*(4), 481–488.

Barch, D. M., & Ceaser, A. (2012). Cognition in schizophrenia: core psychological and neural mechanisms. *Trends in Cognitive Sciences*, *16*(1), 27–34. http://doi.org/10.1016/j.tics.2011.11.015

Barch, D. M., Pagliaccio, D., & Luking, K. (2015). Mechanisms Underlying Motivational Deficits in Psychopathology: Similarities and Differences in Depression and Schizophrenia. *Current Topics in Behavioral Neurosciences*. http://doi.org/10.1007/7854_2015_376

Beck, S. M., Locke, H. S., Savine, A. C., Jimura, K., & Braver, T. S. (2010). Primary and Secondary Rewards Differentially Modulate Neural Activity Dynamics during Working Memory. *PLoS ONE*, *5*(2), e9251. http://doi.org/10.1371/journal.pone.0009251

Berridge, K. C., & Kringelbach, M. L. (2008). Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology*, *199*(3), 457–480. http://doi.org/10.1007/s00213-008-1099-6

References

Berridge, K. C., & Robinson, T. E. (2003). Parsing reward. *Trends in Neurosciences*, *26*(9), 507–513. http://doi.org/10.1016/S0166-2236(03)00233-9

Berridge, K. C., Robinson, T. E., & Aldridge, J. W. (2009). Dissecting components of reward: “liking”, “wanting”, and learning. *Current Opinion in Pharmacology*, *9*(1), 65–73. http://doi.org/10.1016/j.coph.2008.12.014

Blanchard, J. J., & Cohen, A. S. (2006). The Structure of Negative Symptoms Within Schizophrenia: Implications for Assessment. *Schizophrenia Bulletin*, *32*(2), 238–245. http://doi.org/10.1093/schbul/sbj013

Braver, T. S., Krug, M. K., Chiew, K. S., Kool, W., Westbrook, J. A., Clement, N. J., … Group, for the M. (2014). Mechanisms of motivation–cognition interaction: challenges and opportunities. *Cognitive, Affective, & Behavioral Neuroscience*, *14*(2), 443–472. http://doi.org/10.3758/s13415-014-0300-0

Carlsson, A., & Lindqvist, M. (1963). Effect of Chlorpromazine or Haloperidol on Formation of 3methoxytyramine and Normetanephrine in Mouse Brain. *Acta Pharmacol Toxicol (Copenh)*, *20*, 140–4.

Chiew, K. S., & Braver, T. S. (2011). Positive Affect Versus Reward: Emotional and Motivational Influences on Cognitive Control. *Frontiers in Psychology*, *2*. http://doi.org/10.3389/fpsyg.2011.00279

Cohen, A. S., McGovern, J. E., Dinzeo, T. J., & Covington, M. A. (2014). Speech deficits in serious mental illness: A cognitive resource issue? *Schizophrenia Research*, *160*(1–3), 173–179. http://doi.org/10.1016/j.schres.2014.10.032

Cohen, A. S., Morrison, S. C., Brown, L. A., & Minor, K. S. (2012). Towards a cognitive resource limitations model of diminished expression in schizotypy. *Journal of Abnormal Psychology*, *121*(1), 109–118. http://doi.org/10.1037/a0023599

Corlett, P. R., Murray, G. K., Honey, G. D., Aitken, M. R. F., Shanks, D. R., Robbins, T. W., … Fletcher, P. C. (2007). Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain*, *130*(9), 2387–2400. http://doi.org/10.1093/brain/awm173

References

Cox, K. M., & Kable, J. W. (2014). BOLD Subjective Value Signals Exhibit Robust Range Adaptation. *The Journal of Neuroscience*, *34*(49), 16533–16543. http://doi.org/10.1523/JNEUROSCI.3927-14.2014

Deserno, L., Boehme, R., Heinz, A., & Schlagenhauf, F. (2013). Reinforcement Learning and Dopamine in Schizophrenia: Dimensions of Symptoms or Specific Features of a Disease Group? *Frontiers in Psychiatry*, *4*. http://doi.org/10.3389/fpsyt.2013.00172

Erhart, S. M., Marder, S. R., & Carpenter, W. T. (2006). Treatment of Schizophrenia Negative Symptoms: Future Prospects. *Schizophrenia Bulletin*, *32*(2), 234–237. http://doi.org/10.1093/schbul/sbj055

Foussias, G., & Remington, G. (2010). Negative Symptoms in Schizophrenia: Avolition and Occam's Razor. *Schizophrenia Bulletin*, *36*(2), 359–369. http://doi.org/10.1093/schbul/sbn094

Gold JM, Waltz JA, Matveeva TM, & et al. (2012). Negative symptoms and the failure to represent the expected reward value of actions: Behavioral and computational modeling evidence. *Archives of General Psychiatry*, *69*(2), 129–138. http://doi.org/10.1001/archgenpsychiatry.2011.1269

Gold, J. M., Waltz, J. A., Prentice, K. J., Morris, S. E., & Heerey, E. A. (2008). Reward Processing in Schizophrenia: A Deficit in the Representation of Value. *Schizophrenia Bulletin*, *34*(5), 835–847. http://doi.org/10.1093/schbul/sbn068

Grimm, O., Heinz, A., Walter, H., Kirsch, P., Erk, S., Haddad, L., … Meyer-Lindenberg, A. (2014). Striatal response to reward anticipation: evidence for a systems-level intermediate phenotype for schizophrenia. *JAMA Psychiatry*, *71*(5), 531–539. http://doi.org/10.1001/jamapsychiatry.2014.9

Häfner, H. (2000). Onset and early course as determinants of the further course of schizophrenia. *Acta Psychiatrica Scandinavica. Supplementum*, (407), 44–48.

Heckers, S., Barch, D. M., Bustillo, J., Gaebel, W., Gur, R., Malaspina, D., … Carpenter, W. (2013). Structure of the psychotic disorders classification in DSM-5. *Schizophrenia Research*, *150*(1), 11–14. http://doi.org/10.1016/j.schres.2013.04.039

References

Hemsley, D. R. (2005). The Schizophrenic Experience: Taken Out of Context? *Schizophrenia Bulletin*, *31*(1), 43–53. http://doi.org/10.1093/schbul/sbi003

Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., … Heinz, A. (2006). Dysfunction of ventral striatal reward prediction in schizophrenia. *NeuroImage*, *29*(2), 409–416. http://doi.org/10.1016/j.neuroimage.2005.07.051

Kapur, S. (2003). Psychosis as a State of Aberrant Salience: A Framework Linking Biology, Phenomenology, and Pharmacology in Schizophrenia. *American Journal of Psychiatry*, *160*(1), 13–23. http://doi.org/10.1176/appi.ajp.160.1.13

Kennerley, S. W., & Wallis, J. D. (2009). Reward-Dependent Modulation of Working Memory in Lateral Prefrontal Cortex. *The Journal of Neuroscience*, *29*(10), 3259–3270. http://doi.org/10.1523/JNEUROSCI.5353-08.2009

Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *21*(16), RC159.

Knutson, B., Fong, G. W., Adams, C. M., Varner, J. L., & Hommer, D. (2001). Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport*, *12*(17), 3683–3687.

Knutson, B., & Heinz, A. (2015). Probing psychiatric symptoms with the monetary incentive delay task. *Biological Psychiatry*, *77*(5), 418–420. http://doi.org/10.1016/j.biopsych.2014.12.022

Kobayashi, S., Carvalho, O. P. de, & Schultz, W. (2010). Adaptation of Reward Sensitivity in Orbitofrontal Neurons. *The Journal of Neuroscience*, *30*(2), 534–544. http://doi.org/10.1523/JNEUROSCI.4009-09.2010

Krawczyk, D. C., Gazzaley, A., & D’Esposito, M. (2007). Reward modulation of prefrontal and visual association cortex during an incentive working memory task. *Brain Research*, *1141*, 168–177. http://doi.org/10.1016/j.brainres.2007.01.052

Krebs, R. M., Boehler, C. N., Roberts, K. C., Song, A. W., & Woldorff, M. G. (2012). The Involvement of the Dopaminergic Midbrain and Cortico-Striatal-Thalamic Circuits in the Integration of Reward Prospect and Attentional Task Demands. *Cerebral Cortex*, *22*(3), 607–

615. http://doi.org/10.1093/cercor/bhr134

Kringelbach, M. L., & Berridge, K. C. (2009). Towards a functional neuroanatomy of pleasure and happiness. *Trends in Cognitive Sciences*, *13*(11), 479–487. http://doi.org/10.1016/j.tics.2009.08.006

Leeuw, M. de, Kahn, R. S., & Vink, M. (2015). Fronto-striatal Dysfunction During Reward Processing in Unaffected Siblings of Schizophrenia Patients. *Schizophrenia Bulletin*, *41*(1), 94–103. http://doi.org/10.1093/schbul/sbu153

Locke, H. S., & Braver, T. S. (2008). Motivational influences on cognitive control: Behavior, brain activation, and individual differences. *Cognitive, Affective, & Behavioral Neuroscience*, *8*(1), 99–112. http://doi.org/10.3758/CABN.8.1.99

Manoach, D. S. (2003). Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophrenia Research*, *60*(2–3), 285–298. http://doi.org/10.1016/S0920-9964(02)00294-3

McClure, S. M., York, M. K., & Montague, P. R. (2004). The Neural Substrates of Reward Processing in Humans: The Modern Role of fMRI. *The Neuroscientist*, *10*(3), 260–268. http://doi.org/10.1177/1073858404263526

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews*, *30*, 67–76. http://doi.org/10.1093/epirev/mxn001

Messinger, J. W., Trémeau, F., Antonius, D., Mendelsohn, E., Prudent, V., Stanford, A. D., & Malaspina, D. (2011). Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. *Clinical Psychology Review*, *31*(1), 161–168. http://doi.org/10.1016/j.cpr.2010.09.002

Morris, R., Griffiths, O., Pelley, M. E. L., & Weickert, T. W. (2013). Attention to Irrelevant Cues Is Related to Positive Symptoms in Schizophrenia. *Schizophrenia Bulletin*, *39*(3), 575–582. http://doi.org/10.1093/schbul/sbr192

Morris, R. W., Vercammen, A., Lenroot, R., Moore, L., Langton, J. M., Short, B., … Weickert, T. W. (2012). Disambiguating ventral striatum fMRI-related BOLD signal during reward prediction in schizophrenia. *Molecular Psychiatry*, *17*(3), 235, 280–289. http://doi.org/10.1038/mp.2011.75

Mueser, K. T., & McGurk, S. R. (2004). Schizophrenia. *Lancet (London, England)*, *363*(9426), 2063–2072. http://doi.org/10.1016/S0140-6736(04)16458-1

Murray, G. K., Cheng, F., Clark, L., Barnett, J. H., Blackwell, A. D., Fletcher, P. C., … Jones, P. B. (2008). Reinforcement and reversal learning in first-episode psychosis. *Schizophrenia Bulletin*, *34*(5), 848–855. http://doi.org/10.1093/schbul/sbn078

Murray, G. K., Corlett, P. R., Clark, L., Pessiglione, M., Blackwell, A. D., Honey, G., … Fletcher, P. C. (2007). Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Molecular Psychiatry*, *13*(3), 267–276. http://doi.org/10.1038/sj.mp.4002058

Nielsen, M. Ø., Rostrup, E., Wulff, S., Bak, N., Lublin, H., Kapur, S., & Glenthøj, B. (2012). Alterations of the Brain Reward System in Antipsychotic Naïve Schizophrenia Patients. *Biological Psychiatry*, *71*(10), 898–905. http://doi.org/10.1016/j.biopsych.2012.02.007

Park, S. Q., Kahnt, T., Talmi, D., Rieskamp, J., Dolan, R. J., & Heekeren, H. R. (2012). Adaptive coding of reward prediction errors is gated by striatal coupling. *Proceedings of the National Academy of Sciences*, *109*(11), 4285–4289. http://doi.org/10.1073/pnas.1119969109

Pessoa, L. (2008). On the relationship between emotion and cognition. *Nature Reviews Neuroscience*, *9*(2), 148–158. http://doi.org/10.1038/nrn2317

Pessoa, L. (2009). How do emotion and motivation direct executive control? *Trends in Cognitive Sciences*, *13*(4), 160–166. http://doi.org/10.1016/j.tics.2009.01.006

Pessoa, L., & Engelmann, J. B. (2010). Embedding Reward Signals into Perception and Cognition. *Frontiers in Neuroscience*, *4*. http://doi.org/10.3389/fnins.2010.00017

Rowe, J. B., Eckstein, D., Braver, T., & Owen, A. M. (2008). How Does Reward Expectation Influence Cognition in the Human Brain? *Journal of Cognitive Neuroscience*, *20*(11), 1980–1992. http://doi.org/10.1162/jocn.2008.20140

References

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Archives of General Psychiatry*, *64*(10), 1123–1131. http://doi.org/10.1001/archpsyc.64.10.1123

Schlagenhauf, F., Juckel, G., Koslowski, M., Kahnt, T., Knutson, B., Dembler, T., … Heinz, A. (2008). Reward system activation in schizophrenic patients switched from typical neuroleptics to olanzapine. *Psychopharmacology*, *196*(4), 673–684. http://doi.org/10.1007/s00213-007-1016-4

Schultz, S. K., & Andreasen, N. C. (1999). Schizophrenia. *Lancet (London, England)*, *353*(9162), 1425–1430.

Schultz, W. (2000). Multiple reward signals in the brain. *Nature Reviews. Neuroscience*, *1*(3), 199–207. http://doi.org/10.1038/35044563

Schultz, W. (2013). Updating dopamine reward signals. *Current Opinion in Neurobiology*, *23*(2), 229–238. http://doi.org/10.1016/j.conb.2012.11.012

Schultz, W. (2015). Neuronal Reward and Decision Signals: From Theories to Data. *Physiological Reviews*, *95*(3), 853–951. http://doi.org/10.1152/physrev.00023.2014

Sescousse, G., Caldú, X., Segura, B., & Dreher, J.-C. (2013). Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *37*(4), 681–696. http://doi.org/10.1016/j.neubiorev.2013.02.002

Simon, J. J., Biller, A., Walther, S., Roesch-Ely, D., Stippich, C., Weisbrod, M., & Kaiser, S. (2010). Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression. *Schizophrenia Research*, *118*(1–3), 154–161. http://doi.org/10.1016/j.schres.2009.11.007

Strauss, G. P., Frank, M. J., Waltz, J. A., Kasanova, Z., Herbener, E. S., & Gold, J. M. (2011). Deficits in Positive Reinforcement Learning and Uncertainty-Driven Exploration Are Associated with Distinct Aspects of Negative Symptoms in Schizophrenia. *Biological Psychiatry*, *69*(5), 424–431. http://doi.org/10.1016/j.biopsych.2010.10.015

References

Strauss, G. P., & Gold, J. M. (2012). A new perspective on anhedonia in schizophrenia. *The American Journal of Psychiatry*, *169*(4), 364–373. http://doi.org/10.1176/appi.ajp.2011.11030447

Strauss, G. P., Hong, L. E., Gold, J. M., Buchanan, R. W., McMahon, R. P., Keller, W. R., … Kirkpatrick, B. (2012). Factor structure of the brief negative symptom scale. *Schizophrenia Research*, *142*(1–3), 96–98. http://doi.org/10.1016/j.schres.2012.09.007

Strauss, G. P., Waltz, J. A., & Gold, J. M. (2013). A Review of Reward Processing and Motivational Impairment in Schizophrenia. *Schizophrenia Bulletin*, sbt197. http://doi.org/10.1093/schbul/sbt197

Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., … Carpenter, W. (2013). Definition and description of schizophrenia in the DSM-5. *Schizophrenia Research*, *150*(1), 3–10. http://doi.org/10.1016/j.schres.2013.05.028

Tobler, P. N., Fiorillo, C. D., & Schultz, W. (2005). Adaptive Coding of Reward Value by Dopamine Neurons. *Science*, *307*(5715), 1642–1645. http://doi.org/10.1126/science.1105370

Van Os, J., & Kapur, S. (2009). Schizophrenia. *Lancet*, *374*(9690), 635–45.

Van Rossum, J. M. (1966). The significance of dopamine-receptor blockade for the mechanism of action of neuroleptic drugs. *Arch Int Pharmacodyn Ther*, *160*(2), 492–4.

Vassena, E., Silvetti, M., Boehler, C. N., Achten, E., Fias, W., & Verguts, T. (2014). Overlapping Neural Systems Represent Cognitive Effort and Reward Anticipation. *PLoS ONE*, *9*(3), e91008. http://doi.org/10.1371/journal.pone.0091008

Waltz, J. A., & Gold, J. M. (2007). Probabilistic reversal learning impairments in schizophrenia: Further evidence of orbitofrontal dysfunction. *Schizophrenia Research*, *93*(1–3), 296–303. http://doi.org/10.1016/j.schres.2007.03.010

Waltz, J. A., Schweitzer, J. B., Ross, T. J., Kurup, P. K., Salmeron, B. J., Rose, E. J., … Stein, E. A. (2010). Abnormal Responses to Monetary Outcomes in Cortex, but not in the Basal Ganglia, in Schizophrenia. *Neuropsychopharmacology*, *35*(12), 2427–2439. http://doi.org/10.1038/npp.2010.126

References

Ziauddeen, H., & Murray, G. K. (2010). The relevance of reward pathways for schizophrenia. *Current Opinion in Psychiatry*, *23*(2), 91–96. http://doi.org/10.1097/YCO.0b013e328336661b

Appendix A: Study 1

Kirschner, M., Hager, O. M., Bischof, M., Hartmann, M. N., Kluge, A., Seifritz, E., ... & Kaiser, S. (2015). Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia. *J Psychiatry Neurosci*, *40*, 140383.

Appendix

Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia

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Key words: apathy, functional magnetic resonance imaging, negative symptoms, reward processing, schizophrenia, ventral striatum

Number of words: Abstract 255 words, main text 4349 words.
Number of figures: 4; Number of tables: 2; Number of Supplement: 1

Abstract:

Background: Negative symptoms of schizophrenia can be grouped in two dimensions - apathy and diminished expression. Increasing evidence suggests that negative symptoms are associated with altered neural activity of subcortical and cortical regions in the brain reward system. However, the neurobiological basis of the distinct symptom dimensions within negative symptoms is still poorly understood. The primary aim of the study was to examine the neural correlates of the negative symptom dimensions apathy and diminished expression during a reward processing task.

Methods: 27 patients with schizophrenia and 25 healthy controls underwent event-related fMRI while performing a variant of the monetary incentive delay task. Negative symptom dimensions were assessed with the Brief Negative Symptom Scale.

Results: Both groups showed neural activation indicated by BOLD signal in the ventral striatum during reward anticipation. Ventral striatal activation during reward anticipation showed a strong negative correlation with apathy. Importantly, this effect was not driven by cognitive ability, medication, depressive or positive symptoms. In contrast, no significant correlation with the diminished expression dimension was observed.

Limitations: Although the results remain significant when controlling for chlorpromazine equivalents, we cannot fully exclude potential confounding effects of medication with atypical antipsychotics.

Conclusions: The specific correlation of ventral striatal hypoactivation during reward anticipation with apathy demonstrates a differentiation of apathy and diminished expression on a neurobiological level and provides strong evidence for different pathophysiological mechanisms underlying these two negative symptom dimensions. Our findings contribute to a multilevel framework, in which apathy and motivational impairment in schizophrenia can be described on psychopathological, behavioral and neural levels.

1. Introduction

Negative symptoms are core symptoms of schizophrenia (SZ) and include avolition, anhedonia, asocialty, blunted affect and alogia [1,2]. They contribute strongly to poor functional outcome and reduced subjective quality of life [3–5]. Despite these consequences, current knowledge about the underlying pathophysiology remains limited, hindering the development of effective treatment strategies.

There is now a consensus that negative symptoms can be grouped into two dimensions [2,5,6]. First, a motivational dimension, which we refer to as apathy, combines anhedonia, avolition, and asociality. Second, a diminished expression dimension includes blunted affect and alogia. Importantly, it has been suggested that different neurobiological mechanisms may underlie these dimensions, which would be highly relevant for identifying specific treatment strategies [1,7,8].

Apathy can be defined as reduction of motivation and goal-directed behavior [9,10]. Several behavioral studies have shown that motivational impairments in schizophrenia are associated with dysfunctional processing of reward information in effort-based decision making [11,12], reinforcement learning and during reward anticipation [13,14]. On the neural level, the ventral striatum (VS) appears to play an important role in coding of incentive motivation [15,16] or “wanting” of a reward [17]. There is now consistent evidence for striatal dysfunction during reward anticipation in individuals with schizophrenia and their relatives [18–22]. Importantly, several research groups have found an association between negative symptom severity and reduced activation in the VS, although there are some divergent findings [23–30]. Additionally a relationship between negative symptoms and reduced activity in the dorsal striatum during reward processing and cognitive processing tasks were observed [31,32]. Two studies including our own suggest that ventral striatal hypoactivation might be more strongly related to apathy than global negative symptoms [28,29]. Data from a positron emission tomography study showing an inverse correlation between dopamine levels within the VS and apathy support this idea [33]. However, in prior studies a clear distinction between neurobiological correlates of apathy and diminished expression was not demonstrated. This might be due to several reasons: Previous research mainly focused on total negative symptom scores or concentrated on neurobiological correlates of apathy alone. Finally, relatively small samples likely made it difficult to disentangle between apathy and diminished expression. [34].

The primary aim of the present study was to investigate the specific association between apathy and diminished expression and neural correlates of reward processing in individuals with schizophrenia. We used the new Brief Negative Symptom Scale (BNSS) [35] to assess these two psychopathological dimensions. To investigate the neural activity during anticipation of reward we employed a variant of the Monetary Incentive Delay Task [15]. We hypothesized that apathy but not diminished expression is associated with hypofunction in the VS during reward anticipation. In addition, since a role for the orbitofrontal cortex (OFC) in the pathophysiology of negative symptoms has been suggested [14], we investigated the association between OFC activation during reward outcome processing and the negative symptom dimensions in an exploratory analysis.

2. Methods and Materials

2.1. Participants

Initially, 30 patients with schizophrenia (SZ) and 28 healthy control participants (HC) were included. 5 participants (2 SZ, 3 HC) were excluded because of head movement and one participant with schizophrenia was excluded due to signal dropout in functional images, resulting in a sample of 27 patients and 25 healthy controls. Participants with schizophrenia were recruited from outpatient (n = 11) and inpatient (n = 16) units of the Psychiatric Hospital of the University of Zurich or from institutions affiliated with the Psychiatric Hospital. All patients with schizophrenia were clinically stable and received a stable dose of medication (for further details, see Supplementary Methods 1.1.). The project was approved by the local ethics committee of the canton of Zurich. All participants gave written informed consent to participate in the study. The capability to give informed consent of each participant with schizophrenia was evaluated by the treating psychiatrist.

Diagnosis of schizophrenia was confirmed in a structured Mini-International Neuropsychiatric Interview for DSM-IV [36]. We excluded participants with any other DSM-IV axis I disorder (in particular current substance use disorder and major depressive disorder), medication with lorazepam higher than 1mg, florid psychotic symptoms, i.e. any positive subscale item score higher than four as measured with the Positive and Negative Syndrome Scale (PANSS) [37], and extrapyramidal side effects, i.e. a total score higher than two on the Modified Simpson-Angus Scale (MSAS) [38]. Healthy controls were screened for any neuropsychiatric disorders using the structured Mini-International Neuropsychiatric Interview [36] to ensure that they had no previous or present psychiatric illness. Both study groups - patients and healthy controls - were required to have a normal physical and neurological status and no history of major head injury or neurological disorder.

2.2. Clinical and Neuropsychological Assessment

In order to assess negative symptom dimensions, the BNSS [35] was administered to participants with schizophrenia. The apathy (motivation and pleasure) dimension score included avolition, asociality and anhedonia, while the diminished expression dimension score included alogia and blunted affect (for further details, see Supplementary Methods 1.2). Further psychopathological assessment included the Scale for the Assessment of Negative Symptoms (SANS) [39], the PANSS, the Calgary Depression Scale for Schizophrenia (CDSS) [40], the Global Assessment of Functioning scale (GAF) [41], and the Personal and Social Performance Scale (PSP) [42]. Moreover, both groups performed a neuropsychological test battery assessing different cognitive domains (for further details, see Supplementary Methods 1.2).

2.3. Experimental Design and Task

We used a variant of the Monetary Incentive Delay Task (MID) [15] with stimuli based on the Cued-Reinforcement Reaction Time Task [43]. This variant allowed us to investigate reward anticipation and reward outcome, which was directly dependent on the individual task performance (Figure 1). Before starting the experiment all participants were informed that they would receive the complete amount of money won during the two experimental sessions. At the beginning of each trial, one of three different cues was presented for 0.75 s. The cue indicated the maximum possible amount participants could gain in that trial, i.e. 2

Swiss Francs (CHF), 0.40 CHF, or 0 CHF (1 CHF = 1.08 US $). After a delay, varying from 2.5 to 3 s, the participants had to identify an outlier from three presented circles and press a button (either left or right) as fast as possible (varying from 0.32 to 1 s). Immediately, participants were notified of the amount of money they had won (duration of feedback 2 s). Error trials were defined as trials with a wrong response or late response (after 1s). In all other trials we calculated the actual amount of money to be won for each trial on the basis of the response times of the previous 15 individual trials (Figure S1 in Supplemental Information). This approach was used in order to account for individual differences in response time and thus ensure constant and high rewards in both groups. The maximum amount of money to be won was 50 CHF. Every participant performed two training runs, one outside and one inside the scanner. Excluding the training sessions, the experiment contained two runs with 36 trials of about 10 s each. The inter trial interval (ITI) was jittered from 1 to 9 s with a mean of 3.5 s to enhance statistical power. In total, one run lasted about 6 min. The task was implemented using the MATLAB toolboxes Cogent 2000 and Cogent Graphics.

2.4. Functional Image Acquisition

Imaging data was collected with a Philips Achieva 3.0T magnetic resonance (MR) scanner using a 32 channel SENSE head coil (Philips, Best, The Netherlands) at the MR Zentrum of the Psychiatric Hospital, University of Zurich. Functional MRI (fMRI) was acquired in two runs with 195 images in each run. We used a gradient-echo T2*-weighted echo-planar image (EPI) sequence with 38 slices acquired in ascending order. Acquired in-plane resolution was 3 × 3mm^2, 3mm slice thickness and 0.5 mm gap width over a field of view of 240 × 240 mm, a repetition/echo time (TR/TE) of 2000/25ms and a flip angle of 82°. The first five scans were discarded to eliminate the influence of T1 saturation effects. Slices were aligned with the anterior–posterior commissure. Anatomical data was acquired with an ultrafast gradient echo T1-weighted sequence in 160 sagittal plane slices of 240 × 240 mm resulting in 1 x 1 x 1 mm voxels.

2.5. Data Analyses

All demographic, clinical, neuropsychological and behavioral data, as well as the correlations were analyzed using IBM SPSS Statistics Version 22. Normal distribution was tested with the Kolmogorov-Smirnov Test. We analyzed fMRI data using SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK).

2.5.1. Behavioral Data Analyses

The main behavioral outcome measure was response time, defined as time between target presentation and pressing the correct answer button. We performed a two-way repeated measures analysis of variance (ANOVA) with group as between-subject factor and reward condition (neutral, low, high) as within-subject factor. We performed Mauchly’s test for the assumption of sphericity. In case of violations of the assumption of sphericity we reported Greenhouse Geyser corrected degrees of freedom. As post-hoc tests for significant main effects, we applied Bonferroni corrected pairwise comparisons.

Furthermore, we performed correlation analysis between negative symptom factors and reward-related speeding. Reward-related speeding was calculated by subtracting the response time during the neutral condition (CHF 0) from the response time during the high reward condition (CHF 2.0) divided by the mean of these two conditions.

Potential group differences in all other behavioral data were investigated using two sample t-tests. For non-normally distributed data Mann-Whitney U tests were applied.

2.5.2. Image Preprocessing

Functional images were corrected for differences in the time of slice acquisition and motion using the realign and unwarp function of SPM8. A voxel displacement map, calculated from double phase and magnitude field map data, was used to correct for combined static and dynamic distortions. We performed segmentation, bias correction, and spatial normalization. Finally, images were smoothed using a Gaussian kernel of 6 mm width at half maximum. To assure adequate quality of fMRI Data subjects with translational head movement > 3mm or extensive signal dropout in the EPI sequences were excluded. Following previous studies from van Dijk and Satterthwaite et al. range of motion were calculated as mean relative displacement (MRD) and used for subsequent analyses [44,45]. Mean MRD did not differ significantly between healthy controls (mean MRD = .11, SD = .03) and patients with schizophrenia (mean MRD = .11, SD = .04) (p = .43).

2.5.3. First and Second Level Image Analyses

We used a general linear model (GLM) approach to assess our data in an event-related design at the first level. For the three different reward anticipation phases separate regressors were included: anticipation of no reward (CHF 0), anticipation of low reward (CHF 0.40) and anticipation of high reward (CHF 2.0). For the outcome phases we included one regressor for each condition (three basic regressors). Additionally, for the low (CHF 0.40) and high reward condition (CHF 2.0) the two outcome regressors were parametrically modulated by the actual outcome amount of each trial. Target presentation (one regressor) and anticipation, target and outcome phase in error trials (three regressors) were modelled as regressors of no interest. In total, the first level model included twelve regressors. The canonical hemodynamic response function was used for convolving all explanatory variables. For reward anticipation we calculated the contrast anticipation of high reward (CHF 2.0) versus anticipation of no reward (CHF 0). For the analysis of the outcome processing phase, we used the parametric modulator for high reward (CHF 2.0). At the second level of analysis, we included the individual contrast images of all participants in a random-effects model. We calculated within-group activation using a one sample t-test and between-group activation using a two sample t-test.

2.5.4. Region of Interest Image Analysis

In line with our a priori hypothesis, we defined the VS as region of interest (ROI) during anticipation of reward. Coordinates for the VS were derived from a meta-analysis of Knutson et al. (left: x = -12, y = 10, z = -2; right: x = 0, y= 8, z = 0) investigating previous fMRI studies using the MID task [46]. This approach was adopted from a recent study of Yip et al. who investigated ventral striatal activity in patients with bipolar disorder [47]. . In addition to the VS, we defined the medial orbitofrontal cortex (mOFC) as region of interest for analysis of activation during the outcome phase. The mOFC ROI was constructed as an anatomical voxel mask with the Individual Brain Atlases using Statistical Parametric Mapping (IBASPM

71) [48] implemented in the WFU Toolbox [49]. The statistical thresholds were set at a p = .05 voxel-level family-wise error (FWE) rate correction of p = .05 for multiple comparison in each ROI. Mean percent signal changes were extracted for all voxels in the VS and mOFC ROI using the REX toolbox (http://web.mit.edu/swg/software.htm).

2.5.5. Correlation Analysis

We tested our main hypothesis by calculating bivariate Pearson correlations (r) between negative symptoms (apathy and diminished expression) and percent signal change in the VS and mOFC. Partial correlations were calculated to control for potential confounding variables. Finally, we performed the Steiger test for dependent correlation coefficients to test for potential differences between these correlations [50].

3. Results

3.1. Sample Characteristics

Participant demographics, clinical data and group comparisons are summarized in Table 1. In line with previous research, the two negative symptom dimensions apathy and diminished expression correlated significantly ($r = .45$, $p < .02$) [12].

3.2. Behavioral Data

Regarding response time the repeated measures ANOVA revealed no significant main effect of group [$F(1, 50) = 2.6$, $p = .12$], but a significant main effect of reward [$F(1.4, 69) = 34.0$, $p < .001$]. Post hoc pairwise comparison of the response time showed significant differences between all three conditions (all ps = <.001). Participants were significantly faster in low vs no, high vs low and high vs no reward condition (Figure S2 in Supplemental Information). These results indicate intact reward-related speeding in both groups. There was no significant group X reward interaction effect [$F(1.4, 69) = .65$, $p = .47$]. Furthermore, reward-related speeding did not correlate significantly with apathy ($r = -.22$, $p = .26$) or diminished expression ($r = .02$, $p = .9$). Additionally, to control for differences in cognition, we performed an analysis of covariance with the composite cognitive ability score as covariate, which did not change the significance levels in the repeated measures ANOVA.

Because of low error rates in all three conditions we used total error rates for group comparison. We did not find any differences between healthy controls and patients with schizophrenia ($U = 313.5$, $p = .66$, see Table 2). Finally, differences in total gain were significant ($t = 2.1$, $p = .04$), but small (Table 2).

3.3. Functional Imaging Data

3.3.1. Anticipation of Reward: VS

We focused on brain activation during anticipation of high reward versus no reward. Our a priori defined region of interest was the VS. Healthy controls (left VS: cluster size = 428, t = 5.72; right VS: cluster size = 398, t = 5.60, both p < .05, FWE corrected) and patients with schizophrenia (left VS: cluster size = 259, t =5.44; right VS: cluster size = 361, t = 5.42, both p < .05 FWE corrected) showed significantly stronger activation in the VS during anticipation of high reward as compared to anticipation of no reward (Figure 2). However, in the group comparison we did not find any significant differences during anticipation of high reward versus no reward either in the left or in the right VS. Importantly, all significance level remained unchanged when including the composite cognitive ability score as covariate.

3.3.2. Correlation between Anticipation of Reward and Negative Symptoms

Regarding our primary hypothesis we found a highly significant negative correlation between percent signal change in VS during reward anticipation and apathy in the left VS (r = -.47, p = .01) (Figure 3) and in the right VS (r = -.38, p = .05). Thus, a higher apathy score was associated with less ventral striatal activation during anticipation of high reward in relation to anticipation of no reward. In contrast, no significant correlation between diminished expression and percent signal change in the VS during reward anticipation was observed in the left VS (r = -.001, p = .997) (Figure 3) and right VS (r = .09, p = .65). These correlation coefficients were significantly different from each other (left VS: tDiff = 2.40, p = .02; right VS: tDiff = 2.32, p = .02), i.e. apathy was more strongly associated with reduced ventral striatal activation than diminished expression. Additionally, we performed whole brain voxelwise exploratory correlation analyses revealing no additional cluster showing significant correlation of apathy or diminished expression with activation during reward anticipation.

None of the potential confounding variables such as chlorpromazine equivalents (left VS: r = -.05, p = .82; right VS: r = .01 p = .95), depressive symptoms (CDSS) (left VS: r = .45, p = .02; right VS: r =.34, p =.08), positive symptoms (PANSS positive factor) (left VS: r = -.23, p = .26; right VS: r = -.17, p = .4), cognition (composite cognitive ability score) (left VS: r = .05, p = .8, right VS: r = .12, p = .5) and total amount of gain (left VS r = .22, p = .27; right VS: r = .28, p = .16) were significantly associated with reduced ventral striatal activation. Furthermore, we computed partial correlations to include these potential confounding variables in our main analyses, i.e. the correlations between ventral striatal activation and apathy/diminished expression. The association between apathy and percent signal change in the left VS remained highly significant (r = -.52, p = .01) but not in the right VS (r = -.38, p = .08), when including all covariates stated above. In contrast, the correlation between diminished expression and percent signal change in the VS remained non-significant (left VS: r = -.16, p = .46; right VS: r = .15, p =.5). Importantly, neither VS activation nor apathy scores were related to the range of motion during data acquisition (MRD) (see Supplement table S1). Additionally, an exploratory analysis of correlations between VS activation and all BNSS items and additional psychopathological assessment measures were performed (Table S2, Table S3). Interestingly, these data revealed that the association of apathy with reduced VS activation was strongest for the avolition subscale (left VS: r = -.53, p <.01; right VS r = -.44, p <.05).

3.3.3. Reward Outcome Processing: VS, mOFC

Significant ventral striatal activation related to reward magnitude were observed in patients with schizophrenia (left VS: cluster size = 40, t = 4.4; right VS: cluster size = 31 t = 4.2 both p < .05, FWE corrected) but not in healthy controls. Group comparison showed a significant differences in ventral striatal activation in the right VS (cluster size = 38, t = 4.4, p <.05 FWE corrected). In contrast, healthy controls and patients exhibited significant activation in the mOFC associated with reward magnitude (HC: cluster size = 39, t = 4.5; SZ: cluster size =

400, t = 4.9, both p < .05, FWE corrected) (Figure 4). The group comparison did not reveal any significant differences in the reward responses in the mOFC. Importantly, all significance level remained unchanged when including composite the cognitive ability score as covariate.

3.3.4. Correlation between Outcome Processing and Negative Symptoms

There were no significant correlations between the two negative symptom dimensions and VS or mOFC responses to reward magnitude. Furthermore, we observed no significant association between reduced activations of these regions and positive or depressive symptoms.

4. Discussion

In line with our a priori hypothesis we observed a strong association of reduced striatal activation during reward anticipation with apathy but not with diminished expression. To our knowledge, this is the first study showing a differentiation of apathy and diminished expression on a neurobiological level. At a behavioral level, previous work by our own group and others employing effort based decision making has already provided evidence for different pathophysiological mechanisms underlying the two main negative symptom dimensions [11,12,51]. In a recent study, motivational deficits in schizophrenia, as measured by a progressive ratio task, were associated with clinical amotivation and neural hypoactivation of the VS [30]. The present study extends this work by providing a specific link between the clinical expression of apathy and dysfunctional striatal reward anticipation, which strongly supports the hypothesis of different neural bases for apathy and diminished expression [34]. In this context, our present findings highlight the importance of assessing both negative symptom domains separately when investigating the neural basis of negative symptoms [1,7,8,34].

For the study of apathy it is crucial to account for secondary negative symptoms, which are related to medication side effects, as well as positive psychotic and depressive symptoms [52,53]. We aimed to reduce the potential influence of secondary negative symptoms on our main findings with the following approach: First, we excluded patients at high risk of displaying secondary negative symptoms, i.e. all patients were clinically stable and showed no signs of major depression, no more than moderate positive symptoms and no signs of any extrapyramidal side effects. Second, none of the measures for potential causes of secondary negative symptoms were significantly correlated with ventral striatal activation. Third, the negative correlation between apathy and ventral striatal activation remained highly significant after controlling for all covariates. In addition, the association of apathy and reduced ventral striatal activation was also not influenced by cognitive ability.

Importantly, the negative association with apathy was strongly related to the VS during reward anticipation. A correlation of apathy with activation related to the magnitude of received reward was neither observed in the VS nor in the mOFC. Preclinical studies have consistently emphasized that neurotransmission in the midbrain dopamine system, particularly the projections to the dorsal and ventral striatum mediates incentive motivation or "wanting" of reward [17,34,54]. Furthermore, dopamine depletion or antagonism in the VS leads animals to choose a high effort option for larger rewards less often even though preferences for larger rewards remain intact in the absence of effort requirements [34,55]. Conversely, administration of amphetamine in the VS, or genetic mutations, amplifying the extracellular dopamine levels, contribute to an increase in “wanting” and motivated behavior [56,57]. Human fMRI studies have shown a critical role of the ventral striatal activation during reward anticipation and its relationship to negative symptoms in schizophrenia [23,23,25,27–29]. Now, our findings directly demonstrate for the first time that the association of VS hypofunction with apathy is significantly stronger than the association with diminished expression. Hence, we argue that hypoactivation in the VS reflects a disrupted “wanting” of reward, which contributes to a reduction of motivated behavior and is eventually expressed as apathy on the clinical and psychopathological level.

At the group level, there were no significant differences between patients with schizophrenia and healthy controls in neural activation in the VS during reward anticipation, which is in line with most but not all previous studies [18,24,25,28,29]. One potential explanation of this observation is the fact that all patients in our study were treated with atypical antipsychotics. Thus, our findings are in line with results of Schlagenhauf and colleagues emphasizing an improvement of reduced ventral striatal activity in patients on atypical but not on typical antipsychotics and of Juckel and colleagues showing reduced VS activation in patients treated with typical but not atypical antipsychotics [18,24]. Furthermore, our results suggest an alternative explanation. We observed that neural activity in the VS during reward anticipation is negatively correlated with the severity of apathy in schizophrenia. Thus, patients with low expression of apathy may have intact neural activity in the VS during reward anticipation, which in turn limits the observed difference in group comparisons.

Our finding of an intact mOFC response during receipt of reward is in line with previous imaging studies [19,27,28]. Furthermore, we did not find any association of mOFC activation with the apathy dimension. This could be interpreted as an “intact in-the-moment experience” or “hedonic response” in apathy as recently proposed by various authors [14,58]. However, it has to be acknowledged that our task was not designed to assess whether a prefrontal hypofunction contributes to apathy in addition to ventral striatal dysfunction.

4.1. Limitations

Although the present results provide strong evidence of the association of ventral striatal dysfunction during reward anticipation and apathy in schizophrenia, it is important to note some limitations. First, to fully support the hypothesis of different neural bases of apathy and diminished expression, a double dissociation would have to include neural correlates of diminished expression in addition to those for apathy presented here. Second, although in our analyses antipsychotic dose did not have any statistical effect, it would be important to investigate whether our findings can be generalized to unmedicated patients and patients treated with first generation antipsychotics. Third, screening for potential causes of secondary negative symptoms led to low variance in positive and depressive symptoms, which might be responsible for the lack of an association of these symptoms with reduced ventral striatal activation during reward anticipation. Thus, specificity with respect to these symptom dimensions cannot be inferred from the present study. Likewise, the positive correlation of depressive symptoms with ventral striatal activity during reward anticipation has to be considered in the light of this limitation and should not be overinterpreted. Concerning the analyses of the reward outcome we have to acknowledge that the MID task often does not produce robust neural signal of the VS during the outcome phase as observed in healthy controls in the present study. Therefore, our finding of a lack of correlation between ventral striatal activation related to reward outcomes and apathy should not be overinterpreted.

4.2. Conclusions

In conclusion, the specific correlation of ventral striatal hypoactivation and apathy provides strong evidence for different underlying pathophysiological mechanisms of the two negative symptom domains. Our findings contribute to a multilevel framework, in which apathy and motivational impairment can be described on psychopathological, behavioral and neural levels as proposed in the Research Domain Criteria approach [59]. Ventral striatal hypoactivation could be a potential “neuroimaging marker” for pharmacological treatment trials aiming at negative symptoms, which could help to further elucidate the mechanisms underlying treatment effects.

5. References

1. Kirkpatrick B, Fenton WS, Carpenter WT Jr, et al. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull* 2006;32:214–9.

2. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophr Bull* 2006;32:238–45.

3. Milev P, Ho BC, Arndt S, et al. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. *Am J Psychiatry* 2005;162:495–506.

4. Strauss GP, Harrow M, Grossman LS, et al. Periods of recovery in deficit syndrome schizophrenia: a 20-year multi-follow-up longitudinal study. *Schizophr Bull* 2010;36:788–99.

5. Strauss GP, Horan WP, Kirkpatrick B, et al. Deconstructing negative symptoms of schizophrenia: avolition-apathy and diminished expression clusters predict clinical presentation and functional outcome. *J Psychiatr Res* 2013;47:783–90.

6. Foussias G, Remington G. Negative Symptoms in Schizophrenia: Avolition and Occam’s Razor. *Schizophr Bull* 2010;36:359–69.

7. Messinger JW, Tremeau F, Antonius D, et al. Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. *Clin Psychol Rev* 31:161–8.

8. Liemburg E, Castelein S, Stewart R, et al. Two subdomains of negative symptoms in psychotic disorders: established and confirmed in two large cohorts. *J Psychiatr Res* 2013;47:718–25.

9. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991;38:143–62.

10. Brown RG, Pluck G. Negative symptoms: the “pathology” of motivation and goal-directed behaviour. *Trends Neurosci* 2000;23:412–7.

11. Gold JM, Strauss GP, Waltz JA, et al. Negative Symptoms of Schizophrenia Are Associated with Abnormal Effort-Cost Computations. *Biol Psychiatry* 2013;74:130–6.

12. Hartmann MN, Hager OM, Reimann AV, et al. Apathy But Not Diminished Expression in Schizophrenia Is Associated With Discounting of Monetary Rewards by Physical Effort. *Schizophr Bull* 2014;sbu102.

13. Barch DM, Dowd EC. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. *Schizophr Bull* 2010;36:919–34.

14. Strauss GP, Waltz JA, Gold JM. A Review of Reward Processing and Motivational Impairment in Schizophrenia. *Schizophr Bull* 2014;40:S107–16.

15. Knutson B, Westdorp A, Kaiser E, et al. FMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage* 2000;12:20–7.

16. Knutson B, Gibbs SEB. Linking nucleus accumbens dopamine and blood oxygenation. *Psychopharmacology (Berl)* 2007;191:813–22.

17. Berridge KC, Robinson TE. Parsing reward. *Trends Neurosci* 2003;26:507–13.

18. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. *Psychopharmacol Berl* 2006;187:222–8.

19. Nielsen MØ, Rostrup E, Wulff S, et al. Alterations of the Brain Reward System in Antipsychotic Naïve Schizophrenia Patients. *Biol Psychiatry* 2012;71:898–905.

20. Morris RW, Vercammen A, Lenroot R, et al. Disambiguating ventral striatum fMRI-related bold signal during reward prediction in schizophrenia. *Mol Psychiatry* 2012;17:280–9.

21. De Leeuw M, Kahn RS, Vink M. Fronto-striatal Dysfunction During Reward Processing in Unaffected Siblings of Schizophrenia Patients. *Schizophr Bull* 2014.

22. Grimm O, Heinz A, Walter H, et al. Striatal response to reward anticipation: evidence for a systems-level intermediate phenotype for schizophrenia. *JAMA Psychiatry* 2014;71:531–9.

23. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage* 2006;29:409–16.

24. Schlagenhauf F, Juckel G, Koslowski M, et al. Reward system activation in schizophrenic patients switched from typical neuroleptics to olanzapine. *Psychopharmacol Berl* 2008;196:673–84.

25. Waltz JA, Schweitzer JB, Gold JM, et al. Patients with Schizophrenia have a Reduced Neural Response to Both Unpredictable and Predictable Primary Reinforcers. *Neuropsychopharmacology* 2008;34:1567–77.

26. Wolf DH, Turetsky BI, Loughead J, et al. Auditory Oddball fMRI in Schizophrenia: Association of Negative Symptoms with Regional Hypoactivation to Novel Distractors. *Brain Imaging Behav* 2008;2:132–45.

27. Dowd EC, Barch DM. Anhedonia and emotional experience in schizophrenia: neural and behavioral indicators. *Biol Psychiatry* 2010;67:902–11.

28. Simon JJ, Biller A, Walther S, et al. Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression. *Schizophr Res* 2010;118:154–61.

29. Waltz JA, Schweitzer JB, Ross TJ, et al. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. *Neuropsychopharmacology* 2011;35:2427–39.

30. Wolf DH, Satterthwaite TD, Kantrowitz JJ, et al. Amotivation in Schizophrenia: Integrated Assessment With Behavioral, Clinical, and Imaging Measures. *Schizophr Bull* 2014;sbu026.

31. Ehrlich S, Yendiki A, Greve DN, et al. Striatal function in relation to negative symptoms in schizophrenia. *Psychol Med* 2012;42:267–82.

32. Mucci A, Dima D, Soricelli A, et al. Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. *Psychol Med* 2015;1–14.

33. Kegeles LS, Abi-Dargham A, Frankle WG, et al. Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Arch Gen Psychiatry* 2010;67:231–9.

34. Salamone JD, Koychev I, Correa M, et al. Neurobiological basis of motivational deficits in psychopathology. *Eur Neuropsychopharmacol* [Internet] [cited 2014 Sep 29]; Available from: http://www.sciencedirect.com/science/article/pii/S0924977X1400248X

35. Kirkpatrick B, Strauss GP, Nguyen L, et al. The brief negative symptom scale: psychometric properties. *Schizophr Bull* 2011;37:300–5.

36. Lecrubier Y, Weiller E, Herugeta T, et al. *Mini International Neurpsychiatric Interview German Version 5.0.0*. München: Psychiatrischen Universitätsklinik München; 1999.

37. Kay SR, Opler LA, Lindenmayer JP. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl* 1989;59–67.

38. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970;212:11–9.

39. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. *Arch Gen Psychiatry* 1982;39:784–8.

40. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophr Res* 1990;3:247–51.

41. Frances A, Pincus HA, First MB. The Global Assessment of Functioning Scale (GAF). Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.; 1994.

42. Juckel G, Schaub D, Fuchs N, et al. Validation of the Personal and Social Performance (PSP) Scale in a German sample of acutely ill patients with schizophrenia. *Schizophr Res* 2008;104:287–93.

43. Cools R, Blackwell A, Clark L, et al. Tryptophan depletion disrupts the motivational guidance of goal-directed behavior as a function of trait impulsivity. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol* 2005;30:1362–73.

44. Van Dijk KRA, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage* 2012;59:431–8.

45. Satterthwaite TD, Wolf DH, Loughead J, et al. Impact of in-scanner head motion on multiple measures of functional connectivity: Relevance for studies of neurodevelopment in youth. *NeuroImage* 2012;60:623–32.

46. Knutson B, Greer SM. Anticipatory affect: neural correlates and consequences for choice. *Philos Trans R Soc B Biol Sci* 2008;363:3771–86.

47. Yip SW, Worhunsky PD, Rogers RD, et al. Hypoactivation of the Ventral and Dorsal Striatum During Reward and Loss Anticipation in Antipsychotic and Mood Stabilizer-Naive Bipolar Disorder. *Neuropsychopharmacology* 2015;40:658–66.

48. Alemán-Gómez Y., Melie-García L., Valdés-Hernandez. P. IBASPM: Toolbox for automatic parcellation of brain structures . Presented at the 12th Annual Meeting of the Organization for Human Brain Mapping, June 11-15, 2006, Florence, Italy. Available on CD-Rom in NeuroImage, Vol. 27, No.1.; 2006.

49. Maldjian JA, Laurienti PJ, Kraft RA, et al. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage* 2003;19:1233–9.

50. Steiger JH. Tests for comparing elements of a correlation matrix. *Psychol Bull* 1980;87:245–51.

51. Fervaha G, Graff-Guerrero A, Zakzanis KK, et al. Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making. *J Psychiatr Res* 2013;47:1590–6.

52. Peralta V, Cuesta MJ, Martinez-Larrea A, et al. Differentiating primary from secondary negative symptoms in schizophrenia: a study of neuroleptic-naive patients before and after treatment. *Am J Psychiatry* 2000;157:1461–6.

53. Kirkpatrick B. Developing concepts in negative symptoms: primary vs secondary and apathy vs expression. *J Clin Psychiatry* 2014;75 Suppl 1:3–7.

54. Schultz W. Multiple dopamine functions at different time courses. *Annu Rev Neurosci* 2007;30:259–88.

55. Salamone JD, Correa M, Nunes EJ, et al. The behavioral pharmacology of effort-related choice behavior: dopamine, adenosine and beyond. *J Exp Anal Behav* 2012;97:125–46.

56. Peciña S, Cagniard B, Berridge KC, et al. Hyperdopaminergic mutant mice have higher “wanting” but not “liking” for sweet rewards. *J Neurosci Off J Soc Neurosci* 2003;23:9395–402.

57. Wyvell CL, Berridge KC. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward “wanting” without enhanced “liking” or response reinforcement. *J Neurosci Off J Soc Neurosci* 2000;20:8122–30.

58. Kring AM, Barch DM. The motivation and pleasure dimension of negative symptoms: neural substrates and behavioral outputs. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol* 2014;24:725–36.

59. Cuthbert BN, Insel TR. Toward New Approaches to Psychotic Disorders: The NIMH Research Domain Criteria Project. *Schizophr Bull* 2010;36:1061–2.

Tables

Table 1

Demographic, Psychopathological and Clinical Data

	Patients with Schizophrenia (n = 27)	Healthy Controls (n = 25)	Test Statistic ($t/x^2/U$)	p Value
Age	31.9 (7.1)	33.0 (9.7)	U = 322.00	.78
Gender (f ,m)	9f, 18m	9f, 16m	x^2 = .04	.81
Education, Years	12.2 (3.0)	12.4 (3.6)	U = 334.00	.95
Duration of Illness, Years	9.2 (6.6)			
Age of Onset, Years	22.7 (6)			
Chlorpromazine Equivalents (mg/d)	491.3 (349.5)			
BNSS Apathy (Motivation and Pleasure)	14.8 (6.8)			
BNSS Diminished Expression	9.8 (7.4)			
SANS Apathy *	12.8 (5.1)			
SANS Expression *	12.6 (10.7)			
PANSS Positive Factor †	6.6 (2.5)			
PANSS Negative Factor †	13.6 (5.2)			
PANSS Disorganized Factor †	4.5 (2.2)			
PANSS Excited Factor †	5.1 (1.5)			
PANSS Depressed Factor †	5.1 (2.2)			
PANSS Total †	49.4 (11.2)			
CDSS Total	1.5 (2.2)			
GAF	56.9 (9.6)			
PSP Total	56.4 (9.9)			
Cognition ‡				
Composite Cognitive Ability	-.61 (.89)	0 (.53)	t = 3.0	.01 §
MWT IQ	25.9 (5.8)	27.6 (4.0)	t = 1.2	.23

Note: Data are presented as means and standard deviations. Potential group differences were investigated using 2-sample t-tests for continuous and chi-square tests for categorical data. For non-normally distributed data Mann-Whitney U tests were applied. All patients were receiving atypical antipsychotics at the time of testing. BNSS, Brief Negative Symptom Scale; CDSS, Calgary Depression Scale for Schizophrenia; GAF, Global Assessment of Functioning; MWT IQ, Multiple Word Test Intelligence Quotient; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; SANS, Scale for the Assessment of Negative Symptoms.

* Apathy = Avolition/Apathy, Anhedonia/Asociality; Diminished Expression = Affective Flattening or Blunting, Alogia.

† Positive Factor = P1, P3, P5, G9; Negative Factor = N1, N2, N3, N4, N6, G7; Disorganized Factor = P2, G5, N11; Excited Factor = P4, P7, G8, G14; Depressed Factor = G2, G3, G6

‡ Cognition data have been z-transformed based on the data of the HC group for each test separately. The Composite Cognitive Ability score was computed as the mean of the z-transformed test scores on subject level.

§ $p < .05$

Table 2

Behavioral Data of the Variant of the Monetary Incentive Delay Task

	Patients with Schizophrenia (n = 27)	Healthy Controls (n = 25)	Test Statistic (t/U)	p Value
response time, no reward	555.4 (111.0)	519.2 (81.0)		
response time, low reward	539.4 (106.1)	490.3 (78.6)		
response time, high reward	505.3 (102.7)	467.5 (80.6)		
error trials, total	6.3 (4.4)	5.7 (4.0)	U = 313.5	.66
total gain (in CHF)	36.0 (4.6)	38.9 (5.2)	t = 2.1	.04*

Note: Data are presented as means and standard deviations. Response time is presented in milliseconds. CHF, Swiss Francs. . Potential group differences were investigated using 2-sample t-tests for continuous data. For non-normally distributed data Mann-Whitney U tests were applied.
* p < .05

Appendix

Figures

Figure 1

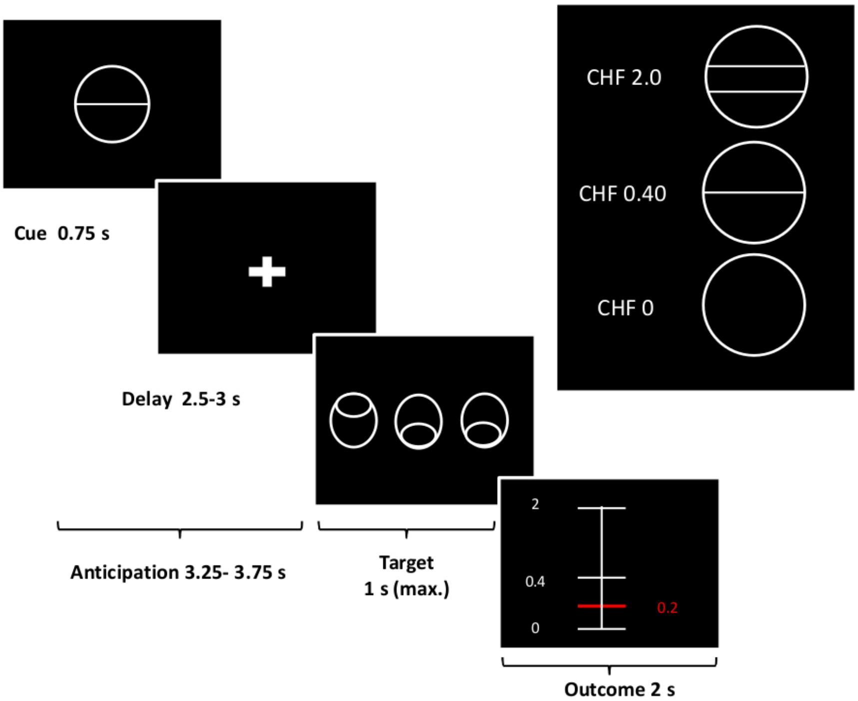

Figure 1. Variant of the Monetary Incentive Delay Task. First, participants saw one of three cues indicating the amount of money they could win, if they reacted correctly during the following discrimination task. Immediately after target presentation, a visual feedback informed the participants about the amount of money they had won during the trial. We used a column ranging from minimal (CHF 0) to maximal win amount (CHF 2.0). A red horizontal line indicated the amount of money won during the respective trial.

Appendix

Figure 2

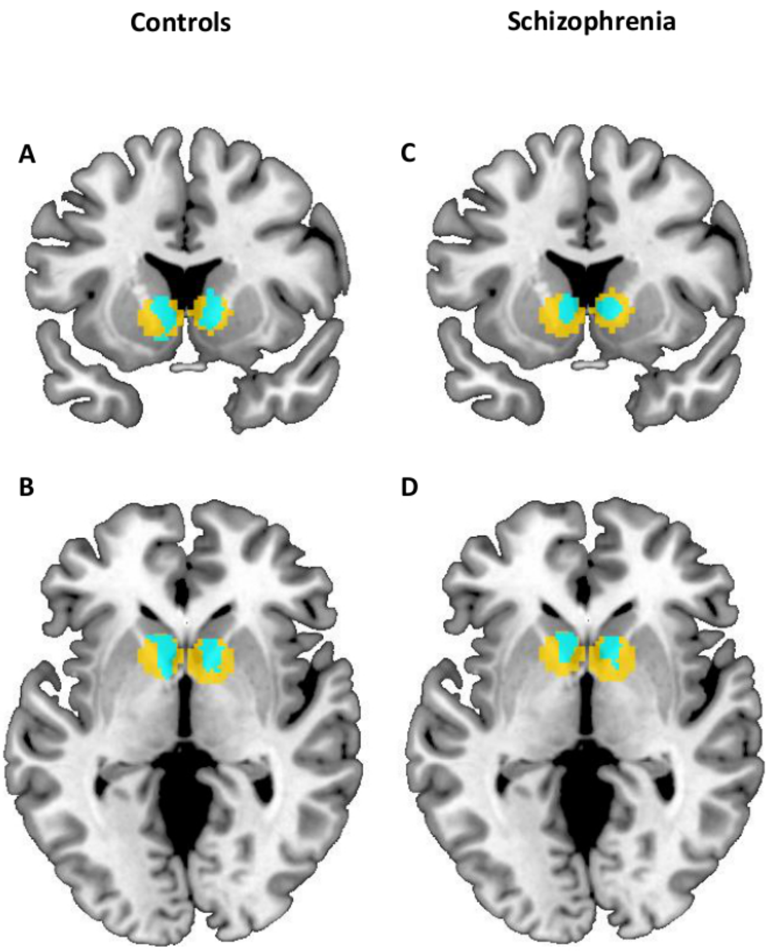

Figure 2. Within group activation maps of the contrast anticipation of high reward vs no reward in the VS (p < .05 FWE corrected). The within group t maps (depicted in cyan) were overlaid on the ROI (shown in dark yellow). (A) Coronal and (B) axial contrast images of healthy controls. (C) Coronal and (D) axial contrast images of participants with schizophrenia.

Appendix

Figure 3

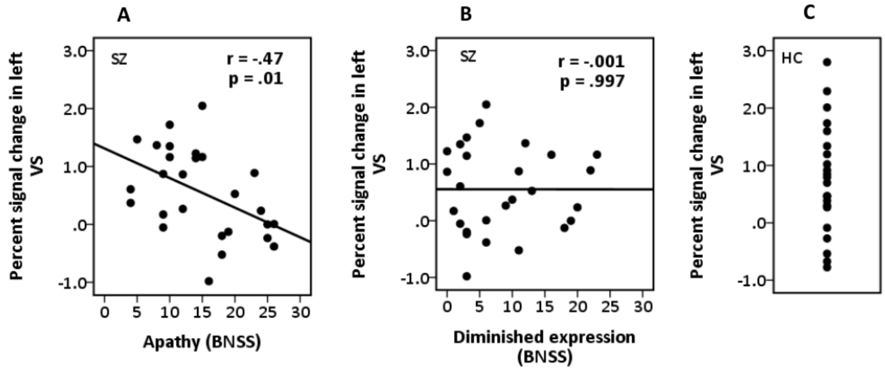

Figure 3. Bivariate Pearson correlation (including significance test) of apathy (A) and diminished expression (B) with percent signal change in the left VS in participants with schizophrenia. Percent signal change in the left VS in healthy controls (C).

Appendix

Figure 4

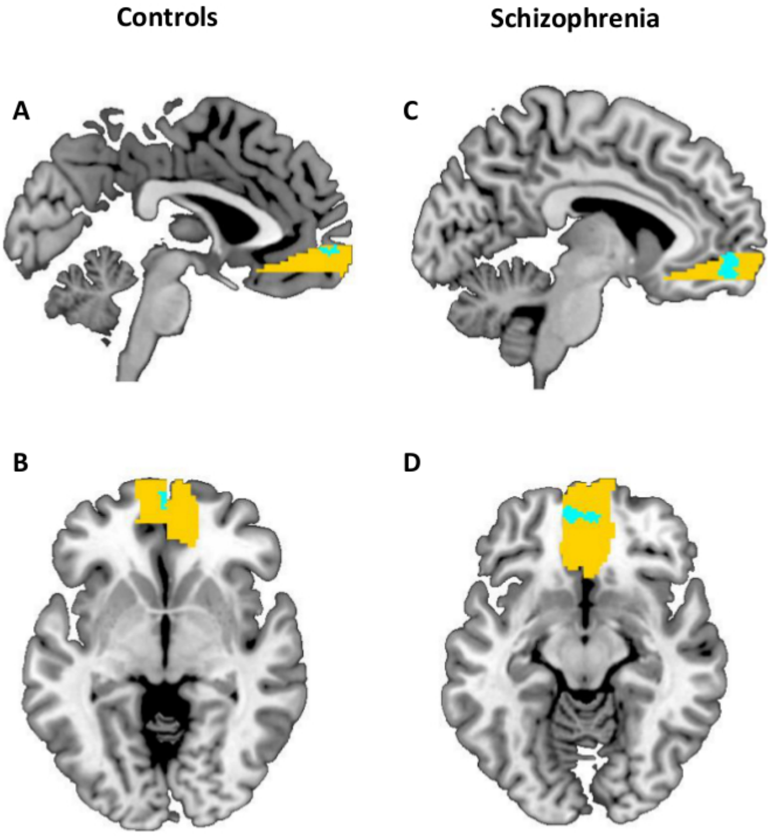

Figure 4. Within group activation maps of the parametric modulator of high reward outcome processing in mOFC (i.e. activation associated with the amount of reward actually received) ($p < .05$ FWE corrected). The within group t maps (depicted in cyan) were overlaid on the ROI (shown in dark yellow). (A) Sagittal (B) axial contrast images of healthy controls. (C) Sagittal and (D) axial contrast images of participants with schizophrenia.

Acknowledgments

This study was supported by the Swiss National Science Foundation (Grant No. 105314_140351 to Stefan Kaiser). Philippe N Tobler was supported by the Swiss National Science Foundation (PP00P1_128574, PP00P1_150739, and CRSII3_141965). We are grateful to Dr. Philipp Staempfli and Dr. Benedikt Habermeyer for their excellent support. We would like to thank all patients and healthy volunteers for their participation.

Financial Disclosures

Stefan Kaiser has received speaker honoraria from Roche, Lundbeck, Janssen and Takeda. He receives royalties for cognitive test and training software from Schuhfried. Erich Seifritz has received grant support from H. Lundbeck and has served as a consultant and/or speaker for AstraZeneca, Otsuka, Eli Lilly, Janssen, Lundbeck, Novartis, Pfizer, Roche, and Servier. None of these activities is related to the present study. All other authors declare no biomedical financial interests or potential conflicts of interest.

Supplementary Materials

Supplementary Methods

1.1 Participants
All inpatients included in the present study were at the end of their hospitalization, participated in a multimodal treatment program and engaged in activities outside the hospital, allowing us to assess negative symptoms. Please note that in Switzerland, the average duration of inpatient treatment of patients with schizophrenia is approximately 40 days [1], which means that most of our inpatients would have been treated as outpatients in other health care systems.

1.2. Clinical and Neuropsychological Assessment
German Version of the BNSS
We used the German Version of the BNSS translated by the senior author and controlled through back-translation to English by a BNSS naïve, English native speaker and psychiatrist. Assessment of inter-rater reliability showed an excellent intra-class correlation coefficient (ICC) of 0.97 for the BNSS total score and ICCs from 0.87 to 0.97 for the subscales.

Neuropsychological test battery
Healthy controls and individuals with schizophrenia performed a neuropsychological test battery assessing verbal learning (Auditory Verbal Learning Memory Test) [2], verbal and visual short-term working memory [3] and corsi block-tapping test [4], processing speed (Digit-Symbol Coding) [5], planning (Tower of London) [6] and semantic and phonetic fluency (animal naming, s-words) [7]. Results of all cognitive tests were summarized in a composite cognitive ability score computed with the mean of z-transformed scores (based on HC group data). Additionally, we used the Multiple Word Test [8] to control for premorbid verbal intelligence.

1.3. Figure S1: Graphical illustration of pay-out structure

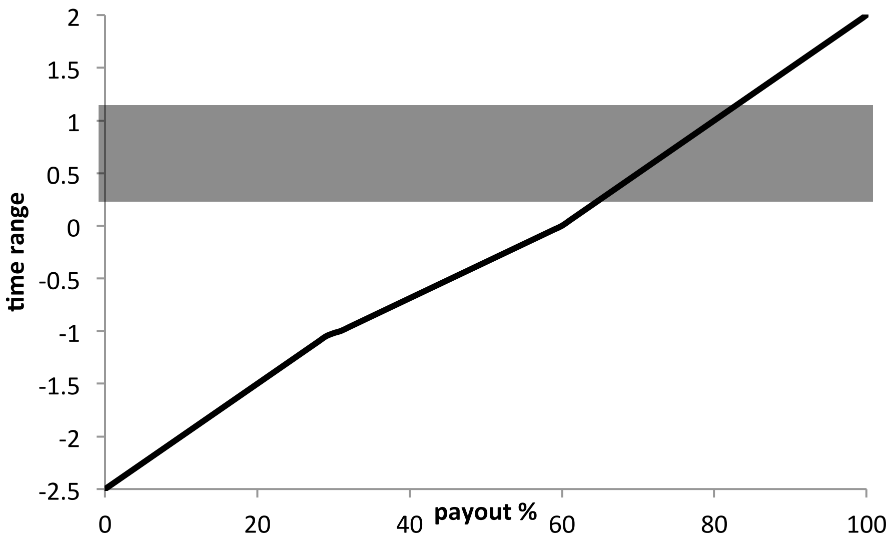

Figure S1. Pay-out structure of variant of the Monetary Incentive Delay task. For every individual we calculated the 15 previous reaction times and sorted them from fast to slow using a simple bubble sorting procedure. We then selected the reaction times corresponding to the 60^{th} percentile and 80^{th} percentile, defining a minimum and maximum of the time range within each participant had to react in order to win money (grey area = time range 0 to 1). Due to the fact that these ranges tended to be low (~5 to 10 milliseconds), we dispersed the time frame, ranging from -2.5 ranges below the original minimum and 1 range above the original maximum. Finally, the pay-out amount was determined by plotting the amount won in each respective trial with this modified dispersion of the original time range. With respect to the pay-out structure this approach allowed the task to possess a “realistic feel” by providing more dispersed outcome amounts. The X-axis represents the corresponding percentage of the maximal possible win during each trial. For example: in order to win CHF 0.8 during the CHF 2 condition, participants had to react -1 ranges below the minimum, in order to win CHF 1.6, the reaction time had to be 1 range above the minimum.

Supplementary Results

2.1. Mean response times and reward-related speeding during experimental conditions

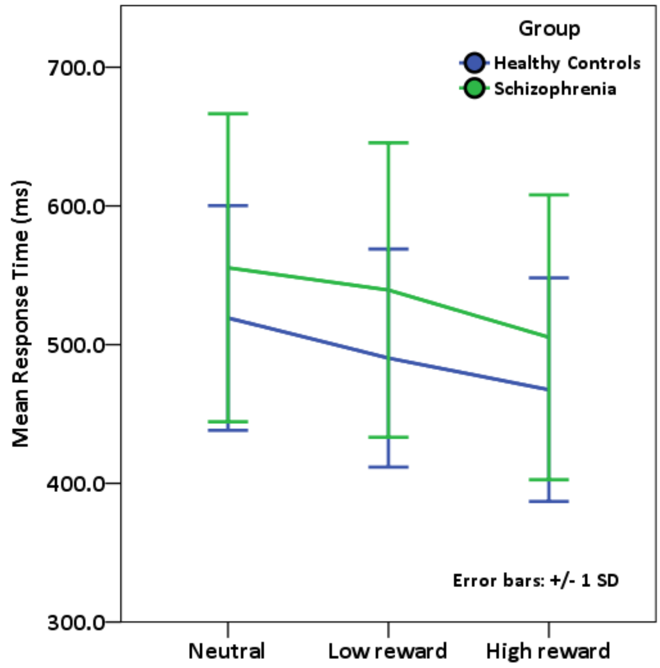

Figure S2. Mean response time (presented in milliseconds) for all three conditions, presented for healthy participants and patients with schizophrenia separately. Data were analyzed using a two-way repeated measures ANOVA with group as between-subject factor and reward condition (neutral, low, high) as within-subject factor.

Table S1. Bivariate correlation of mean relative displacement (MRD) of head motion during data acquisition and ventral striatal activation during reward anticipation and apathy score in individuals with schizophrenia

	MRD (head motion)
Ventral striatal Activation during reward anticipation	
VS left	-.12
VS right	-.08
Psychopathology	
BNSS apathy	.20

Note: According to van Dijk et al.[9] measurement of in-scanner head motion was calculated as mean relative displacement between adjacent volumes. Mean displacement was computed as the root-mean-square of translational parameters (displacement = square root ((x2)+(y2)+(z2)). Number of movements were n-1 (n = 195 volumes).

Table S2. Bivariate correlation of BNSS subscales and individual BNSS items with ventral striatal activation during reward anticipation in individuals with schizophrenia

BNSS subscales and individual items	Percent signal change in left VS during reward anticipation	Percent signal change in right VS during reward anticipation
Anhedonia	**-,29**	**-.25**
BNSS 1	-.27	-.21
BNSS 2	-.25	-.23
BNSS 3	-.32	-.29
Social Withdrawal	**-.33**	**-.22**
BNSS5	-.30	-.17
BNSS6	-.32	-.24
Avolition	**-.53**†	**-.44***
BNSS 7	-.46*	-.36
BNSS 8	-.52†	-.46*
Affective Blunting	**.01**	**.11**
BNSS 9	-.13	-.03
BNSS 10	-.16	-.10
BNSS 11	-.09	-.01
Alogia	**.02**	**.08**
BNSS 12	.02	.08
BNSS 13	.01	.08

*P < .05. †p< .01

Table S3. Bivariate correlation of additional psychopathological and clinical assessment measures with ventral striatal activation during reward anticipation in individuals with schizophrenia

	Percent signal change in left VS during reward anticipation	Percent signal change in right VS during reward anticipation
Psychopathology		
SANS apathy	-.42*	-.26
SANS expression	-.05	.06
PANSS positive factor	-.23	-.17
PANSS negative factor	-.08	.02
CDSS (total)	.45*	.34
GAF (total)	.25	.09
PSP (total)	.16	-.003

Note: Abbreviations are explained in the first footnote to tables 1.
. *P < .05.

To test for potential differences between the two correlations of VS activation and SANS apathy and VS activation and SANS expression we performed the Steiger test for dependent correlation coefficients. We found significant differences between these correlations in the left VS (tDiff = 2.2, p = .03) but not in the right VS (tDiff = 1.8, p = .07).

References

1. BFS. BFS. Medizinische Statistik der Krankenhäuser: Anzahl Fälle und durchschnittliche Aufenthaltsdauer (DAD) nach Altersklasse und Diagnosekode. Neuchatel, Switzerland: BFS; 2012; 2012.

2. Helmstaedter C, Lendt M, Lux S. VLMT. Verbaler Lern- und Merkfähigkeitstest. Göttingen, Germany: Beltz Test GmbH; 2001; 2001.

3. Härting C, Markowitsch HJ, Neufeld H. Wechsler Memory Scale - Revised Edition, German Edition. Manual. Bern, Switzerland: Huber; 2000.

4. Kessels RP, van Zandvoort MJ, Postma A, et al. The Corsi Block-Tapping Task: standardization and normative data. *Appl Neuropsychol* 2000;7:252–8.

5. Von Aster M, Neubauer A, Horn R. *Wechsler Intelligenztest für Erwachsene WIE. Deutschsprachige Bearbeitung und Adaption des WAIS-III von David Wechsler*. Frankfurt, Germany: Pearson Assessment; 2006;

6. Shallice T. Specific impairments of planning. *Philos Trans R Soc Lond B Biol Sci* 1982;298:199–209.

7. Delis DC, Kaplan E, Kramer J. *Delis Kaplan Executive Function System*. San Antonio, TX: The Psychological Corporation; 2001; 2001.

8. Lehrl S, Triebig G, Fischer B. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol Scand* 1995;91:335–45.

9. Van Dijk KRA, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage* 2012;59:431–8.

Appendix B: Study 2

Hager, O. M., Kirschner, M., Bischof, M., Hartmann-Riemer, M. N., Kluge, A., Seifritz, E., ... & Kaiser, S. (2015). Reward-dependent modulation of working memory is associated with negative symptoms in schizophrenia. *Schizophrenia research*, *168*(1), 238-244.

Reward-Dependent Modulation of Working Memory is associated with Negative Symptoms in Schizophrenia

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Word Count:
Abstract: 213
Text: 3061

Abstract:

The negative symptoms of schizophrenia have been associated with altered neural activity during both reward processing and cognitive processing. Even though increasing evidence suggests a strong interaction between these two domains, it has not been studied in relation to negative symptoms. To elucidate neural mechanisms of the reward-cognition interaction, we applied a letter variant of the n-back working memory task and varied the financial incentives for performance. In the interaction contrast, we found a significantly activated cluster in the rostral anterior cingulate cortex (ACC), the middle frontal gyrus, and the bilateral superior frontal gyrus. The interaction did not differ significantly between the patient group and a healthy control group, suggesting that patients with schizophrenia are on average able to integrate reward information and utilize this information to maximize cognitive performance. However within the patient group, we found a significant inverse correlation of ACC activity with the factor diminished expression. This finding is consistent with the model that a lack of available cognitive resources leads to diminished expression. We therefore argue that patients with diminished expression have difficulties in recruiting additional cognitive resources (as implemented in the ACC) in response to an anticipated reward. Due to this lack of cognitive resources, less processing capacity is available for effective expression, resulting in diminished expressive behavior.

Key words: diminished expression, apathy, emotion-cognition interaction, reward anticipation, anterior cingulate cortex

1. Introduction

Negative symptoms – comprising the domains of blunted affect, alogia, asociality, anhedonia, and avolition – are an integral component of schizophrenia. They are a strong predictor of poor prognosis and contribute to functional impairment (Azorin et al., 2014; Kirkpatrick et al., 2006; Milev et al., 2005; Rabinowitz et al., 2012). A recent consensus suggests that negative symptoms can be grouped into two factors. One factor is referred to as diminished expression, comprising blunted affect and alogia. The other factor is referred to as diminished motivation and pleasure, or apathy, and comprises asociality, anhedonia and avolition (Kring and Barch, 2014; Strauss et al., 2012). This distinction might allow a more differentiated approach in the search of underlying pathophysiological mechanisms (Blanchard and Cohen, 2006; Foussias and Remington, 2010; Liemburg et al., 2013; Messinger et al., 2011).

Negative Symptoms have been consistently associated with dysfunctional reward processing, in particular with diminished reward anticipation. On a neural level, this has been linked to a reduction in ventral striatal activity (Juckel et al., 2006; Nielsen et al., 2012; Schlagenhauf et al., 2008; Simon et al., 2010; Waltz et al., 2008). Negative symptoms have also been linked to neurocognitive deficits, although this association is rather modest (Lin et al., 2013; Milev et al., 2005; Ventura et al., 2013, 2009). The cognitive deficits, and to a lesser extent negative symptoms, have been associated with abnormal activity in the prefrontal cortex, particularly the dorsolateral prefrontal cortex (dlPFC; Barch and Ceaser, 2012; Manoach, 2003).

Recent work suggests that there is a strong interaction of reward anticipation with cognitive performance. Knowing that a certain cognitive effort might result in the receipt of a reward leads to the prioritization of the respective process and influences the assignment of limited cognitive resources (Beck et al., 2010; Braver et al., 2014; Kennerley and Wallis, 2009; Krawczyk et al., 2007; Locke and Braver, 2008; Rowe et al., 2008). On the neural level, the anterior cingulate cortex (ACC) has been suggested to play an essential role in this interaction and to act as a hub linking reward and cognition (Krebs et al., 2012; Pessoa, 2009, 2008; Vassena et al., 2014). It is presumed that the ACC receives reward information from the ventral striatum (VS), thereby enhancing cognitive performance (Holroyd and Yeung, 2012; Pessoa, 2009; Steenbergen et al., 2014). It remains unknown how negative symptoms in schizophrenia relate to the reward-cognition interaction at the neural level.

In the current study, we measured cognitive performance with a letter variant of the n-back working memory (WM) task and varied the financial incentives for the performance. We hypothesized that patients with schizophrenia would show impairments in the modulation of cognitive performance by reward and that these impairments are correlated with the severity of negative symptoms. On a neural level, we expected that the prospect of a future reward leads to the activation of the ACC as well as to a stronger activation in WM related regions in the lateral PFC. We expected that these effects are diminished in the patient group and show an inverse correlation with the severity of negative symptoms.

2. Methods

2.1. Participants

We studied 29 individuals meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000) criteria for schizophrenia (n=23) or schizoaffective disorder (n=6) and 27 healthy control subjects with no personal history of a DSM-IV axis 1 disorder. All participants provided written informed consent to participate in the study, which was approved by the local Ethics committee. Patients were recruited either as inpatients (n=16) or outpatients (n=13) from the Psychiatric Hospital, University of Zurich, or from affiliated institutions. All inpatients were at the end of their hospitalization and they participated in a multimodal treatment program that encouraged them to engage in daily activities outside the hospital. All patients received constant doses of medication for at least two weeks prior to testing, with the exception of one patient receiving a small increase of clozapine dose seven days before testing. Exclusion criteria included a daily lorazepam dosage greater than 1mg, florid positive symptoms, i.e. any positive subscale item score of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) >4, extrapyramidal side effects, measured with the Modified Simpson-Angus Scale (MSAS; Simpson et al., 1970), >3, or any other DSM-IV axis 1 diagnosis. For confirmation, all participants were assessed using the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1997).

2.2. Clinical and neuropsychological assessment

All patients were further assessed using the Brief Negative Symptom Scale (BNSS; Strauss et al., 2012), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen NC, 1982), the PANSS, the Global Assessment of Functioning scale (GAF; Frances et al., 1994), the Personal and Social Performance Scale (PSP; Schaub and Juckel, 2011) and the Calgary Depression Scale for Schizophrenia (CDS, Addington et al., 1993). We used the BNSS as our main measurement for negative symptoms since it was designed to facilitate a clear distinction of the factors apathy and diminished expression. For the total BNSS score, the assessment of the inter-rater reliability showed an intra-class correlation coefficient (ICC) of 0.97. The subscales reached ICCs from 0.87 to 0.97.

To characterize the sample and to disentangle the effects of neuropsychological functioning, the following cognitive domains were tested: verbal learning (Auditory Verbal Learning Memory Test, VLMT; Helmstaedter and Durwen, 1990), verbal and visual short-term working memory (Digit Span, DS; Stieglitz, 2000) and Corsi block-tapping test (CBT; Kessels et al., 2000), processing speed (Digit-Symbol Coding, DSC; Von Aster et al., 2006), planning (Tower of London, ToL; Shallice, 1982), and semantic and phonetic fluency (animal naming, AN; s-words, SW; Delis et al., 2001).

2.3. Functional magnetic resonance imaging

2.3.1. Imaging acquisition

Two runs containing 185 whole brain T2* weighted echo-planar images (EPI) were acquired in ascending order using a Philips Achieva 3.0T magnetic resonance scanner with a 32 channel SENSE head coil (Philips, Best, The Netherlands). Further specifications were: 3x3x3mm^3 in-plane resolution, 0.5mm gap width, 240x240mm field of view, 2000ms TR, 25ms TE, flip angle 82°. Slices were aligned with the anterior-posterior commissure. The first five scans were discarded to eliminate the influence of T1 saturation effects. A T1-weighted high-resolution anatomical scan was obtained for registration: 160 sagittal plane slices, 1x1x1mm^3.

2.3.2. Task and stimuli

A modified version of a previously employed letter n-back task was used (Owen et al., 2005; Pochon et al., 2002). The task was presented as a two by two factorial design with the factors cognitive load (0-back vs. 2-back) and reward (reward vs. no reward), resulting in a total of four different conditions: 0-back/reward (0R), 0-back/no reward (0N), 2-back/reward (2R), 2-back/no reward (2N) (see figure 1).

--- Insert figure 1 here ---

2.3.3. Behavioral analyses

The sensitivity index d’ (Haatveit et al., 2010; Green, 1988) and reaction times were used to analyze the behavioral performance. D’ is calculated as the standardized probability of a hit minus the standardized probability of a false alarm: d’ = z(probability(hits)) – z(probability(false alarms)). To test for differences in behavioral performance, d’ and reaction times were entered into separate mixed-design ANOVAs with group (patient group, healthy control group) as between-subjects factor and cognition (0-back, 2-back) and reward (no reward, reward) as within-subject factors. To relate behavioral performance to psychopathological ratings of negative symptoms, we calculated Pearson’s r. All analyses were performed using IBM SPSS Statistics Version 21.

2.3.4. fMRI analyses

Functional MRI data were analyzed using SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK). Differences in EPI slice acquisition timing were corrected using the central slice as reference. To reduce artifacts from head movements, functional images were realigned using a least squares approach and a six-parameter rigid body spatial transformation, using the first image as a reference. A voxel displacement map, calculated from double phase and magnitude field map data, was applied for a combined static and dynamic distortion correction. After co-registration, the “New Segment” toolbox was used for spatial normalization. Finally, images were smoothed using a Gaussian kernel of 6 mm width.

For our block design, we used a general linear model (GLM) with a two-stage approach. On the first stage of analysis, two levels of cognitive load (0-back/2-back) and two levels of reward (reward/no reward) were modeled. To study the cognition/reward interaction effect, i.e., the effect of reward-dependent modulation of working memory, the following contrast images were constructed: ((2-back/reward) – (0-back/reward)) – ((2-back/no reward) – (0-back/no reward)). These images were taken to the second stage of analysis for random-effects inference.

Due to our a priori hypothesis, we restricted our search volume to the PFC and ACC (Barch and Dowd, 2010; Cai and Padoa-Schioppa, 2014; Kaping et al., 2011; Kennerley and Wallis, 2009; Kennerley and Walton, 2011; Watanabe, 2007). We used the Automated Anatomical Labeling (AAL; Tzourio-Mazoyer et al., 2002) atlas implemented in the WFU_PickAtlas toolbox (Maldjian et al., 2004, 2003) for SPM and included the following bilateral regions to construct one single search volume: the dorsolateral and superior frontal gyrus, the (orbital) middle frontal gyrus, the opercular, triangular and orbital inferior frontal gyrus, the medial superior frontal gyrus, and the anterior part of the cingulate gyrus. Within our restricted single volume of interest, the statistical threshold was set to FWEp=0.05. Cluster extend was calculated based on p<.001 uncorrected.

To relate brain activation with psychopathological ratings in the patient group, we extracted mean beta values in the interaction contrast based on the activated clusters in the healthy control group using the REX toolbox (Whitefield-Gabrieli, 2009) and performed simple correlation analyses.

For exploratory purposes we also extracted parameter estimates in the activated clusters in the whole group (i.e. combined patients and controls) interaction contrast and calculated correlations with negative symptoms.

3. Results

3.1. Sample Characteristics

Demographic and clinical data are summarized in table 1. There were no significant group differences with regard to age, gender, handedness, and education. As expected, we found a significant group difference in the composite score of all cognitive tests. The healthy control group performed significantly better than the patient group. However, we found no significant difference in the test scores measuring working memory performance (see below).

--- Insert table 1 here ---

3.2. Behavioral Data

In the n-back task, the main effect of group on sensitivity was not significant, F(1,54)=.955, p=.333. Pooling over all subjects, we found a significant main effect of the factor cognition on sensitivity, F(1,54)=7.514, p=.008. Participants performed significantly better in the 0-back condition ($\bar{x}$=7.05, SD=.61) relative to the 2-back condition ($\bar{x}$=6.65, SD=.93), meaning that the d' is significantly higher in the 0-back condition relative to the 2-back condition. The main effect of the factor reward on accuracy and the interaction of cognition and reward was not significant, F(1,54)=.060, p=.808 and F(1,54)=.338, p=.563, respectively. All other interactions were also non-significant. We did not find any significant correlation between sensitivity and psychopathological ratings.

With regard to reaction times, we found a main effect of group, F(1,54)=4.633, p=.036, indicating that healthy control subjects were faster than patients with schizophrenia across conditions. Furthermore, across all subjects, we found a main effect of the factor cognition, F(1,54)=43.789, p<.001, indicating that participants were significantly faster in the 0-back condition ($\bar{x}$=468.03, SD=65.04) relative to the 2-back condition ($\bar{x}$=546.64, SD=110.63). We also found a main effect of the factor reward, F(1,54)=8.656, p=.005, showing that participants speeded up in the rewarded trials ($\bar{x}$=499.09, SD=81.38) relative to the non rewarded trials ($\bar{x}$=515.58, SD=82.47). The reward-cognition interaction, F(1,54)=.007, p=.935, as well as all other interactions were not significant. Furthermore, we found a significant positive correlation of BNSS apathy with the mean reaction time of the 2back condition relative to the 0back condition (r=.38, p=.042) and with the mean reaction time of the reward-cognition interaction (r=.38, p=.041). All other correlations between reaction time and negative symptom scores were non-significant.

--- Insert table 2 here ---

3.3. Imaging Data

In the whole group reward-cognition interaction contrast, we found significant activation within our volume of interest in the right superior frontal gyrus (rSFG; x=17, y=21, z=58; k=910, t=6.13, FWEp<.001), the left superior frontal gyrus (lSFG; x=-18, y=33, z=42, k=567, t=5.33, FWEp<.001), the right rostral cingulate cortex (rACC; x=9, y=44, z=1, k=1018, t=5.32 FWEp<.001), and the medial superior frontal gyrus (mSFG; x=8, y=68, z=18, k=267, t=5.15, FWEp<.001), when working memory performance was rewarded compared to when it was not rewarded (see figure 2A). These regions could therefore be involved in integrating reward and cognition.

Next we looked at the groups separately and tested for activation differences. Within the healthy control group, we found a cluster in the right rostral anterior cingulate cortex (rACC; x=9, y=44, z=1, k=88; t=5.91, FWEp=.047) that showed significantly more activation in the interaction contrast (see figure 2B). This cluster was further used for our correlation analyses. The according parameter estimates can be found in the supplement (supplementary figure 1). The patient group showed significant activation in the right superior frontal gyrus (rSFG; x=23, y=15, z=55; k=661; t=7.21, FWEp=.002) within this interaction contrast (See figure 2C). However, we did not find any significant differences between the two groups, in line with the absence of a behavioral difference.

In addition to the analysis in our a priori defined volume of interest, we also performed a whole brain analysis using the same statistical thresholds (see supplementary table 1), which did not reveal any additional clusters.

--- Insert Figure 2 here ---

3.4. Correlation analyses

Within the patient group, ACC activation in the reward-cognition interaction contrast correlated negatively with BNSS diminished expression (r(29)=-.393, p=.035). The correlation with SANS diminished expression reached trend-level significance (r(29)=-.365, p=.052). In contrast, the correlation between percent signal change in the ACC and BNSS apathy as well as SANS apathy did not reach significance (r(29)=-.015, p=.937, and r=-.001, p=.998, respectively; see figure 3).

To test for a difference between these two dependent correlations, we performed a Steiger's Z-test, which revealed that the correlation between BNSS diminished expression and percent signal change was significantly different from the correlation between BNSS apathy and percent signal change (Z=-2.04, p=.041). To confirm that other potentially confounding variables, i.e., depressive symptoms, chlorpromazine equivalents, and age, did not account for the correlation between BNSS diminished expression and activity in the ACC, we computed a partial correlation with the factors above included. The association between diminished expression and ACC activation remained significant (r(24)=-.402, p=.042).

--- Insert Figure 3 here ---

Furthermore, we also found a significant correlation of ACC activation and BNSS diminished expression (r(29)=-.434, p=.019) when we defined the clusters based on the whole group (i.e. combined patients and controls) analysis, which underlines the robustness of this finding (see supplementary table 2). No other cluster from the whole group analysis showed a significant correlation with negative symptom dimensions.
We additionally performed an exploratory whole-brain ANCOVA with the standardized BNSS measures (diminished expression and apathy) as covariates in a whole brain analysis, but this analysis did not reveal any significant clusters.

4. Discussion

To our knowledge, this is the first study to investigate the neural effects of reward modulation on working memory in patients with schizophrenia and healthy controls. On the neural level, we found evidence that reward modulation influences working memory in both groups. In the patient group, we found a negative correlation of activity in the ACC with the negative symptom factor diminished expression, but not with the factor apathy.

Across all subjects, our behavioral data suggest that participants processed both cognitive and reward factors of the task. We further found that apathy was significantly correlated with the reaction time in the 2back relative to the 0back condition and in the in the reward-cognition interaction, indicating that cognitive load and the integration of complex information reduces reaction time in apathetic patients. On the neural level, the reward-cognition interaction led, among others, to significant activation of the rostral ACC. This region has been suggested to play an important role in controlling current demands, which are influenced by the presence of a potential reward or punishment (Holroyd and Yeung, 2012; Pessoa, 2009, 2008; Pessoa and Engelmann, 2010; Steenbergen et al., 2014). It is further assumed that the signal from the ACC is used to guide behavior via dense interconnections with cortical areas, such as the (pre-) motor cortex and the DLPFC (Haber and Knutson, 2009). In line with this hypothesis, we also observe three PFC clusters in the reward-cognition interaction contrast, which are part of the working memory network. Due to the reward at stake, the cognitive process leading to the harvest of the reward is prioritized, and cognitive resource capacities are allocated in order to maximize performance. Since we did not find any significant group differences, we believe that this process is generally functioning in patients with schizophrenia, at least at the relatively basic levels tested here.

However, within the patient group, we found a significant inverse correlation of the negative symptom factor diminished expression with activity in the rostral ACC related to the reward-cognition interaction. This correlation was specific for the factor diminished expression, because it was significantly different from the correlation with the factor apathy. The correlation remained significant after controlling for confounding variables. Since the ACC has been proposed to play a crucial role in controlling resource distribution and behavioral adaptation, we hypothesize that patients with more severe negative symptoms, in particular diminished expression, have difficulties in regulating their limited available processing resources to meet the current demand (Holroyd and Yeung, 2012; Pessoa, 2009; Steenbergen et al., 2014).

This idea is in line with the cognitive resource limitation model (Cohen et al., 2012, 2013, 2014a, 2014b). Cohen proposes that effective expression requires a range of mental resources. If these limited resources are engrossed by another task or process, they are not available for expressive behavior. Considering that patients with schizophrenia have lower cognitive abilities compared to healthy controls, the effects are magnified, since fewer resources are available in the first place. Our data suggest that patients with more pronounced diminished expression do not only have less cognitive resources available as proposed by Cohen (2012, 2013, 2014), but that they have a specific problem in adjusting resources according to their priority. In other words, potential reward fails to recruit additional cognitive resources, which in turn leads to diminished expressive behavior.

There are several limitations to our study. Since this was the first study to investigate the neural correlates of reward-cognition interaction, the hypotheses were relatively broad. Thus, the study has to be considered exploratory and requires replication. Furthermore, although the antipsychotic medication did not have any statistical effects, further studies should elucidate whether these results can be generalized to unmedicated patients.

In conclusion, we found a specific inverse correlation of rostral ACC activation with the factor diminished expression. To our knowledge, this is the first study showing a specific correlation of neural activity with this factor, supporting the notion of separable neural bases for the two negative symptom dimensions. These findings highlight the need to further investigate the complex interaction of reward processing and cognition, with a particular focus on the adaptation of cognitive resources in schizophrenia and the relation to diminished expression.

5. References

Addington, D., Addington, J., Maticka-Tyndale, E., 1993. Assessing depression in schizophrenia: The Calgary Depression Scale. Br. J. Psychiatry 163, 39–44.

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders (DSM). Washington, DC.

Andreasen NC, 1982. Negative symptoms in schizophrenia: Definition and reliability. Arch. Gen. Psychiatry 39, 784–788. doi:10.1001/archpsyc.1982.04290070020005

Azorin, J.-M., Belzeaux, R., Adida, M., 2014. Negative Symptoms in Schizophrenia: Where We have been and Where We are Heading. CNS Neurosci. Ther. 20, 801–808. doi:10.1111/cns.12292

Barch, D.M., Ceaser, A., 2012. Cognition in schizophrenia: core psychological and neural mechanisms. Trends Cogn. Sci., Special Issue: Cognition in Neuropsychiatric Disorders 16, 27–34. doi:10.1016/j.tics.2011.11.015

Barch, D.M., Dowd, E.C., 2010. Goal Representations and Motivational Drive in Schizophrenia: The Role of Prefrontal–Striatal Interactions. Schizophr. Bull. 36, 919–934. doi:10.1093/schbul/sbq068

Beck, S.M., Locke, H.S., Savine, A.C., Jimura, K., Braver, T.S., 2010. Primary and Secondary Rewards Differentially Modulate Neural Activity Dynamics during Working Memory. PLoS ONE 5, e9251. doi:10.1371/journal.pone.0009251

Blanchard, J.J., Cohen, A.S., 2006. The Structure of Negative Symptoms Within Schizophrenia: Implications for Assessment. Schizophr. Bull. 32, 238–245. doi:10.1093/schbul/sbj013

Braver, T.S., Krug, M.K., Chiew, K.S., Kool, W., Westbrook, J.A., Clement, N.J., Adcock, R.A., Barch, D.M., Botvinick, M.M., Carver, C.S., Cools, R., Custers, R., Dickinson, A., Dweck, C.S., Fishbach, A., Gollwitzer, P.M., Hess, T.M., Isaacowitz, D.M., Mather, M., Murayama, K., Pessoa, L., Samanez-Larkin, G.R., Somerville, L.H., Group, for the M., 2014. Mechanisms of motivation–cognition interaction: challenges and opportunities. Cogn. Affect. Behav. Neurosci. 14, 443–472. doi:10.3758/s13415-014-0300-0

Cai, X., Padoa-Schioppa, C., 2014. Contributions of Orbitofrontal and Lateral Prefrontal Cortices to Economic Choice and the Good-to-Action Transformation. Neuron 81, 1140–1151. doi:10.1016/j.neuron.2014.01.008

Cohen, A.S., Kim, Y., Najolia, G.M., 2013. Psychiatric symptom versus neurocognitive correlates of diminished expressivity in schizophrenia and mood disorders. Schizophr. Res. 146, 249–253. doi:10.1016/j.schres.2013.02.002

Cohen, A.S., McGovern, J.E., Dinzeo, T.J., Covington, M.A., 2014a. Speech deficits in serious mental illness: A cognitive resource issue? Schizophr. Res. 160, 173–179. doi:10.1016/j.schres.2014.10.032

Cohen, A.S., Mitchell, K.R., Elvevåg, B., 2014b. What do we really know about blunted vocal affect and alogia? A meta-analysis of objective assessments. Schizophr. Res. doi:10.1016/j.schres.2014.09.013

Cohen, A.S., Morrison, S.C., Brown, L.A., Minor, K.S., 2012. Towards a cognitive resource limitations model of diminished expression in schizotypy. J. Abnorm. Psychol. 121, 109–118. doi:10.1037/a0023599

Delis, D., Kaplan, E., Kramer, J., 2001. Delis-Kaplan Executive Function System (D-KEFS). The Psychological Corporation, San Antonio (TX).

Foussias, G., Remington, G., 2010. Negative Symptoms in Schizophrenia: Avolition and Occam's Razor. Schizophr. Bull. 36, 359–369. doi:10.1093/schbul/sbn094

Frances, A., Pincus, H.A., First, M.B., 1994. The global assessment of functioning scale (GAF), in: Diagnostic and Statistical Manual of Mental Disorder IV.

Haber, S.N., Knutson, B., 2009. The Reward Circuit: Linking Primate Anatomy and Human Imaging. Neuropsychopharmacology 35, 4–26. doi:10.1038/npp.2009.129

Helmstaedter, C., Durwen, H.F., 1990. VLMT: Verbaler Lern- und Merkfähigkeitstest: Ein praktikables und differenziertes Instrumentarium zur Prüfung der verbalen Gedächtnisleistungen. Schweiz. Arch. Für Neurol. Psychiatr. 141, 21–30.

Holroyd, C.B., Yeung, N., 2012. Motivation of extended behaviors by anterior cingulate cortex. Trends Cogn. Sci. 16, 122–128. doi:10.1016/j.tics.2011.12.008

Juckel, G., Schlagenhauf, F., Koslowski, M., Wüstenberg, T., Villringer, A., Knutson, B., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenia. NeuroImage 29, 409–416. doi:10.1016/j.neuroimage.2005.07.051

Kaping, D., Vinck, M., Hutchison, R.M., Everling, S., Womelsdorf, T., 2011. Specific Contributions of Ventromedial, Anterior Cingulate, and Lateral Prefrontal Cortex for Attentional Selection and Stimulus Valuation. PLoS Biol 9, e1001224. doi:10.1371/journal.pbio.1001224

Kay, S.R., Flszbein, A., Opfer, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Schizophr. Bull. 13, 261–276.

Kennerley, S.W., Wallis, J.D., 2009. Reward-Dependent Modulation of Working Memory in Lateral Prefrontal Cortex. J. Neurosci. 29, 3259–3270. doi:10.1523/JNEUROSCI.5353-08.2009

Kennerley, S.W., Walton, M.E., 2011. Decision making and reward in frontal cortex: Complementary evidence from neurophysiological and neuropsychological studies. Behav. Neurosci. 125, 297–317. doi:10.1037/a0023575

Kessels, R.P.C., van Zandvoort, M.J.E., Postma, A., Kappelle, L.J., de Haan, E.H.F., 2000. The Corsi Block-Tapping Task: Standardization and Normative Data. Appl. Neuropsychol. 7, 252–258. doi:10.1207/S15324826AN0704_8

Kirkpatrick, B., Fenton, W.S., Carpenter, W.T., Marder, S.R., 2006. The NIMH-MATRICS Consensus Statement on Negative Symptoms. Schizophr. Bull. 32, 214–219. doi:10.1093/schbul/sbj053

Krawczyk, D.C., Gazzaley, A., D'Esposito, M., 2007. Reward modulation of prefrontal and visual association cortex during an incentive working memory task. Brain Res. 1141, 168–177. doi:10.1016/j.brainres.2007.01.052

Krebs, R.M., Boehler, C.N., Roberts, K.C., Song, A.W., Woldorff, M.G., 2012. The Involvement of the Dopaminergic Midbrain and Cortico-Striatal-Thalamic Circuits in the Integration of Reward Prospect and Attentional Task Demands. Cereb. Cortex 22, 607–615. doi:10.1093/cercor/bhr134

Kring, A.M., Barch, D.M., 2014. The motivation and pleasure dimension of negative symptoms: Neural substrates and behavioral outputs. Eur. Neuropsychopharmacol., Negative symptoms of schizophrenia: clinical characteristics and their measurement, experimental modelling, and opportunities for improved treatment 24, 725–736. doi:10.1016/j.euroneuro.2013.06.007

Liemburg, E., Castelein, S., Stewart, R., van der Gaag, M., Aleman, A., Knegtering, H., 2013. Two subdomains of negative symptoms in psychotic disorders: Established and confirmed in two large cohorts. J. Psychiatr. Res. 47, 718–725. doi:10.1016/j.jpsychires.2013.01.024

Lin, C.-H., Huang, C.-L., Chang, Y.-C., Chen, P.-W., Lin, C.-Y., Tsai, G.E., Lane, H.-Y., 2013. Clinical symptoms, mainly negative symptoms, mediate the influence of neurocognition and social cognition on functional outcome of schizophrenia. Schizophr. Res. 146, 231–237. doi:10.1016/j.schres.2013.02.009

Locke, H.S., Braver, T.S., 2008. Motivational influences on cognitive control: Behavior, brain activation, and individual differences. Cogn. Affect. Behav. Neurosci. 8, 99–112. doi:10.3758/CABN.8.1.99

Maldjian, J.A., Laurienti, P.J., Burdette, J.H., 2004. Precentral gyrus discrepancy in electronic versions of the Talairach atlas. NeuroImage 21, 450–455. doi:10.1016/j.neuroimage.2003.09.032

Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 19, 1233–1239. doi:10.1016/S1053-8119(03)00169-1

Manoach, D.S., 2003. Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. Schizophr. Res. 60, 285–298. doi:10.1016/S0920-9964(02)00294-3

Messinger, J.W., Trémeau, F., Antonius, D., Mendelsohn, E., Prudent, V., Stanford, A.D., Malaspina, D., 2011. Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. Clin. Psychol. Rev. 31, 161–168. doi:10.1016/j.cpr.2010.09.002

Milev, P., Ho, B.-C., Arndt, S., Andreasen, N.C., 2005. Predictive Values of Neurocognition and Negative Symptoms on Functional Outcome in Schizophrenia: A Longitudinal First-Episode Study With 7-Year Follow-Up. Am. J. Psychiatry 162, 495–506. doi:10.1176/appi.ajp.162.3.495

Nielsen, M.Ø., Rostrup, E., Wulff, S., Bak, N., Lublin, H., Kapur, S., Glenthøj, B., 2012. Alterations of the Brain Reward System in Antipsychotic Naïve Schizophrenia Patients. Biol. Psychiatry, Altered Functional Connectivity in Schizophrenia 71, 898–905. doi:10.1016/j.biopsych.2012.02.007

Owen, A.M., McMillan, K.M., Laird, A.R., Bullmore, E., 2005. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Hum. Brain Mapp. 25, 46–59. doi:10.1002/hbm.20131

Pessoa, L., 2008. On the relationship between emotion and cognition. Nat. Rev. Neurosci. 9, 148–158. doi:10.1038/nrn2317

Pessoa, L., 2009. How do emotion and motivation direct executive control? Trends Cogn. Sci. 13, 160–166. doi:10.1016/j.tics.2009.01.006

Pessoa, L., Engelmann, J.B., 2010. Embedding Reward Signals into Perception and Cognition. Front. Neurosci. 4. doi:10.3389/fnins.2010.00017

Pochon, J.B., Levy, R., Fossati, P., Lehericy, S., Poline, J.B., Pillon, B., Bihan, D.L., Dubois, B., 2002. The neural system that bridges reward and cognition in humans: An fMRI study. Proc. Natl. Acad. Sci. 99, 5669–5674. doi:10.1073/pnas.082111099

Rabinowitz, J., Levine, S.Z., Garibaldi, G., Bugarski-Kirola, D., Berardo, C.G., Kapur, S., 2012. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: Analysis of CATIE data. Schizophr. Res. 137, 147–150. doi:10.1016/j.schres.2012.01.015

Rowe, J.B., Eckstein, D., Braver, T., Owen, A.M., 2008. How Does Reward Expectation Influence Cognition in the Human Brain? J. Cogn. Neurosci. 20, 1980–1992. doi:10.1162/jocn.2008.20140

Schaub, D., Juckel, G., 2011. PSP-Skala – Deutsche Version der Personal and Social Performance Scale : Validiertes Messinstrument zur Erfassung des psychosozialen Funktionsniveaus in der Schizophrenietherapie (Originalien). Nervenarzt 82, 1178–1184.

Schlagenhauf, F., Juckel, G., Koslowski, M., Kahnt, T., Knutson, B., Dembler, T., Kienast, T., Gallinat, J., Wrase, J., Heinz, A., 2008. Reward system activation in schizophrenic patients switched from typical neuroleptics to olanzapine. Psychopharmacology (Berl.) 196, 673–684. doi:10.1007/s00213-007-1016-4

Shallice, T., 1982. Specific Impairments of Planning. Philos. Trans. R. Soc. B Biol. Sci. 298, 199–209. doi:10.1098/rstb.1982.0082

Sheehan, D., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., Knapp, E., Sheehan, M., Dunbar, G., 1997. The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. Eur. Psychiatry 12, 232–241. doi:10.1016/S0924-9338(97)83297-X

Simon, J.J., Biller, A., Walther, S., Roesch-Ely, D., Stippich, C., Weisbrod, M., Kaiser, S., 2010. Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression. Schizophr. Res. 118, 154–161. doi:10.1016/j.schres.2009.11.007

Simpson, G.M., B., M., B., G., Angus, J.W.S., P., F.R.C., M., D.P., 1970. A Rating Scale for Extrapyramidal Side Effects. Acta Psychiatr. Scand. 45, 11–19. doi:10.1111/j.1600-0447.1970.tb02066.x

Steenbergen, H. van, Band, G.P.H., Hommel, B., Rombouts, S.A.R.B., Nieuwenhuis, S., 2014. Hedonic Hotspots Regulate Cingulate-driven Adaptation to Cognitive Demands. Cereb. Cortex bht416. doi:10.1093/cercor/bht416

Stieglitz, R.-D., 2000. WMS-R. Wechsler Gedächtnistest - revidierte Fassung. Z. Für Klin. Psychol. Psychother. 29, 307–308. doi:10.1026//0084-5345.29.4.307

Strauss, G.P., Hong, L.E., Gold, J.M., Buchanan, R.W., McMahon, R.P., Keller, W.R., Fischer, B.A., Catalano, L.T., Culbreth, A.J., Carpenter, W.T., Kirkpatrick, B., 2012. Factor structure of the brief negative symptom scale. Schizophr. Res. 142, 96–98. doi:10.1016/j.schres.2012.09.007

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. NeuroImage 15, 273–289. doi:10.1006/nimg.2001.0978

Vassena, E., Silvetti, M., Boehler, C.N., Achten, E., Fias, W., Verguts, T., 2014. Overlapping Neural Systems Represent Cognitive Effort and Reward Anticipation. PLoS ONE 9, e91008. doi:10.1371/journal.pone.0091008

Ventura, J., Hellemann, G.S., Thames, A.D., Koellner, V., Nuechterlein, K.H., 2009. Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis. Schizophr. Res. 113, 189–199. doi:10.1016/j.schres.2009.03.035

Ventura, J., Wood, R.C., Hellemann, G.S., 2013. Symptom Domains and Neurocognitive Functioning Can Help Differentiate Social Cognitive Processes in Schizophrenia: A Meta-Analysis. Schizophr. Bull. 39, 102–111. doi:10.1093/schbul/sbr067

Von Aster, M., Neubauer, A., Horn, R., 2006. Wechsler Intelligenztest für Erwachsene (WIE). Deutschsprachige Bearbeitung und Adaptation des WAIS-III von David Wechsler. Harcourt

Test Services, Frankfurt.

Waltz, J.A., Schweitzer, J.B., Gold, J.M., Kurup, P.K., Ross, T.J., Jo Salmeron, B., Rose, E.J., McClure, S.M., Stein, E.A., 2008. Patients with Schizophrenia have a Reduced Neural Response to Both Unpredictable and Predictable Primary Reinforcers. Neuropsychopharmacology 34, 1567–1577. doi:10.1038/npp.2008.214

Watanabe, M., 2007. Role of anticipated reward in cognitive behavioral control. Curr. Opin. Neurobiol., Cognitive neuroscience 17, 213–219. doi:10.1016/j.conb.2007.02.007

Whitefield-Gabrieli, S., 2009. REX Toolbox.

Tables

Table 1

	Patient Group (n = 29)	HC Group (n = 27)	Test Statistic ($t/X^2/U$)	P
Age in years	32.07 (7.26)	33.11 (9.02)	t = .478	.64
Gender (male/female)	20/9	17/10	χ^2 = .225	.64
Formal education in years	12.03 (3.08)	12.35 (3.45)	U = 377.5	.82
Duration of illness in months	174.03 (323.18)	–		
Number of hospitalizations	5.07 (4.36)	–		
Chlorpromazine equivalents (mg/day)	536.76 (400.96)	–		
Psychopathology				
BNSS apathy[a]	14.41 (7.22)	–		
BNSS diminished expression[a]	9.45 (8.06)	–		
SANS apathy[b]	12.14 (5.13)	–		
SANS diminished expression[b]	11.90 (10.78)	–		
PANSS positive factor[c]	6.52 (2.63)	–		
PANSS negative factor[c]	13.74 (5.38)	–		
GAF	57.41 (9.59)	–		
PSP (total)	56.97 (9.81)	–		
CDSS (total)	1.52 (2.18)	–		
Cognition				
Composite cognitive ability[d]	-.45 (.78)	0 (.49)	t = 2.583	**.013**
CBS forward	8.17 (1.81)	8.56 (2.04)	t = .743	.46
CBS backward	7.66 (1.84)	7.96 (1.66)	t = .653	.52
DS forward	7.31 (2.04)	7.59 (1.72)	t = .559	.58
DS backward	6.55 (1.80)	6.22 (1.34)	U = 359.5	.59

Notes: Data are presented as means and standard deviations. For normally distributed continuous and categorical variables, 2-sample t tests and chi-square were applied to test for potential group differences. If data were not normally distributed, Mann-Whitney U tests were applied.

All patients except one were receiving stable doses of atypical antipsychotic medication at the time of testing. Nine individuals were additionally receiving antidepressants, two were receiving mood-stabilizers, two patients were medicated against insomnia and one person was receiving a low dose of benzodiazepine

BNSS, Brief Negative Symptom Scale; SANS, Scale for the Assessment of Negative Symptoms; PANSS, Positive and Negative Syndrome Scale; GAF, General Assessment of Functioning; PSP, Personal and Social Performance Scale; CDSS, Calgary Depression Scale for Schizophrenia; CBS, Corsi block span; DS, Digit span

P values lower than .05 are in bold

[a]Apathy = Anhedonia, Asociality, Avolition; diminished expression = lack of normal distress, blunted affect, alogia

[b]Apathy = Avolition/Apathy, Anhedonia/Asociality; diminished expression = Affective Flattening or blunting, Alogia

[c]Positive factor = P1, P3, P5, G9; negative factor = N1, N2, N3, N4, N6, G7

[d]Cognition data have been standardized based on the HC group

Appendix

Table 2

	Patient Group (n = 29)	HC Group (n = 27)
Accuracy		
0-back Reward	6.95 (.59)	7.13 (.80)
0-back No Reward	7.15 (.48)	6.99 (.92)
2-back Reward	6.48 (1.16)	6.90 (.68)
2-back No Reward	6.54 (1.34)	6.70 (.98)
Reaction Time		
0-back Reward	472.26 (72.88)	445.82 (52.49)
0-back No Reward	495.57 (74.15)	456.14 (59.62)
2-back Reward	564.43 (126.85)	511.02 (106.30)
2-back No Reward	582.33 (109.68)	524.83 (114.86)

Notes: Data are presented as means and standard deviations. Accuracy is measured as the standardized probability of a hit minus the standardized probability of a false alarm. Reaction time is measured in ms.

Figures

Figure 1

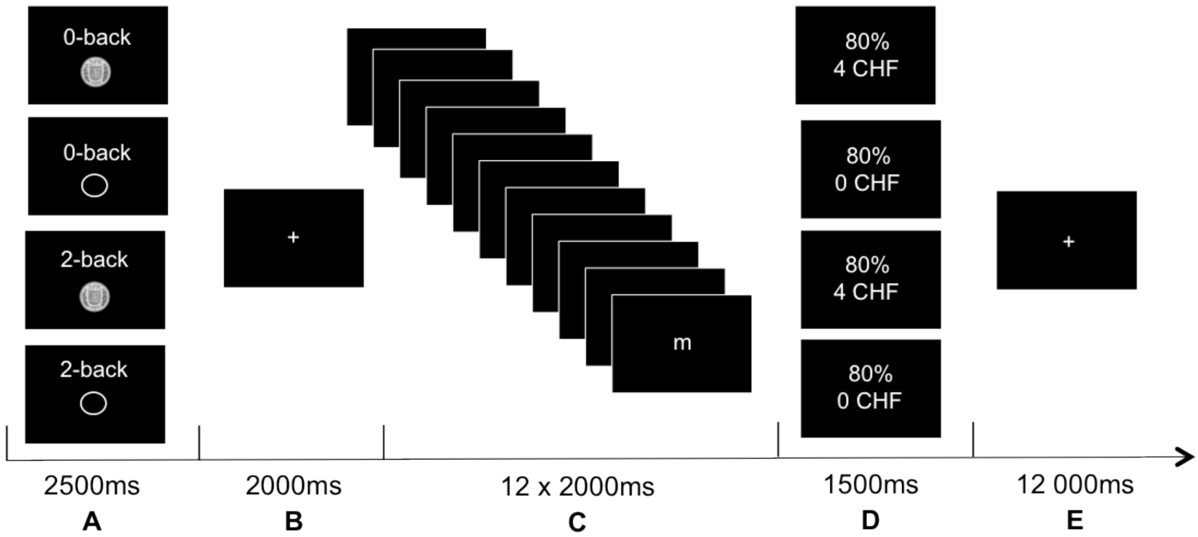


Figure 1. Schematic view of the modified letter n-back task. Each condition was presented four times, resulting in a total of 16 blocks. The 16 blocks were split into 2 runs. The order of presentation was equal for all subjects and as follows: 0R, 2R, 0N, 2N, 2N, 0N, 2R, 0R; 0R, 0N, 2R, 2N, 2N, 2R, 0N, 0R. In the 0-back condition, participants had to press a button whenever a pre-specified letter appeared on the screen, i.e., the letter x. In the 2-back condition, participants were required to press a button whenever the letter they saw was equal to the letter presented before the last one. In the reward condition, participants earned a monetary reward according to their performance. The maximum payment per block was 5 Swiss Francs (CHF) whereas the minimum payment was 0 CHF. The maximum payment for all 8 blocks was 40 CHF. Additionally, participants received a guaranteed amount of 10 CHF. In the no reward condition, the subjects did not receive any payment.

After the indication of the current condition, a fixation cross followed (A & B). One block consisted of 12 letter stimuli containing 4 targets. Each letter appeared for 500ms and was followed by an intertrial interval of 1500ms (C). After the presentation of all 12 stimuli, a feedback about the performance and the monetary gain was given for 2500ms (D). A resting period of 12000ms followed after every block (E).

Figure 2

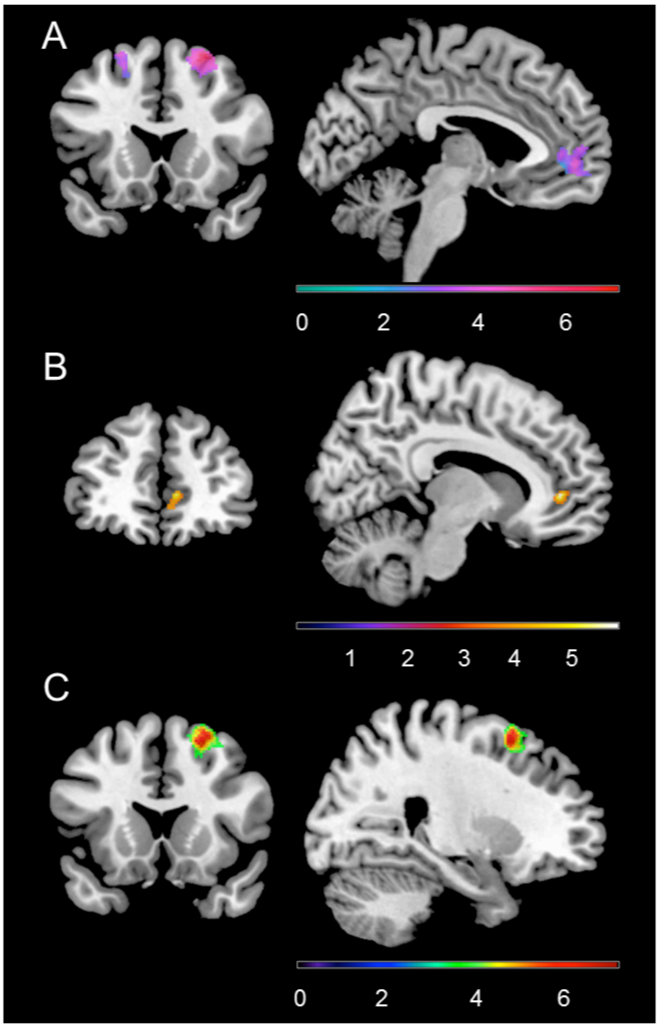


Figure 2. Group activation maps of the contrast rewarded WM vs. non-rewarded WM: ((2-back/reward – 0-back/reward) – (2-back/no reward – 0-back/no reward)) for all subjects (A), healthy controls (B), and patients with schizophrenia (C). The search volume was restricted to the PFC and ACC. Please note that there were no significant differences between groups. The statistical threshold was set FWEp = 0.05. The cluster extend was based on p < .001, uncorrected.

Figure 3

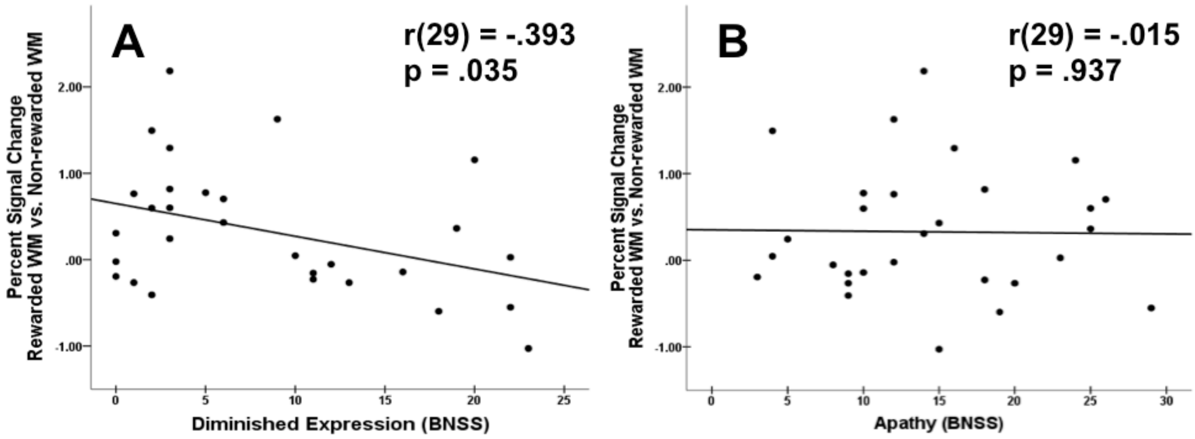


Figure 3. Correlation between percent signal change in the ACC in the interaction contrast and diminished expression scores (A) and apathy scores (B). The two correlations differed significantly from each other, suggesting a stronger relation of diminished expression than apathy to the reward/cognition interaction.

Acknowledgment

We are grateful to Dr. Philipp Staempfli for his excellent technical support. Furthermore, we want to thank Giulia Elsaesser for her support during data collection.

Role of funding source

The study was supported by the Swiss National Science Foundation (Grant No. 105314_140351 to Stefan Kaiser). Philippe N Tobler was supported by the Swiss National Science Foundation (PP00P1_128574, PP00P1_150739, and CRSII3_141965).

Contributors

S. Kaiser, O. Hager, and P. Tobler designed the study. O.M. Hager, M. Kirschner, M. Bischof, A. Kluge, and M.N. Hartmann conducted the study. O. Hager conducted the analyses and wrote the first draft of the manuscript. O. Hager, S. Kaiser, P. Tobler, E. Seifritz revised the manuscript. All authors contributed to and have approved of the final manuscript.

Conflict of Interest

Stefan Kaiser has received speaker honoraria from Roche, Takeda, Janssen and Lundbeck. He receives royalties for cognitive test and training software from Schuhfried. Erich Seifritz has received grant support from H. Lundbeck and has served as a consultant and/or speaker for AstraZeneca, Otsuka, Eli Lilly, Janssen, Lundbeck, Novartis, Pfizer, Roche, and Servier. None of these activities is related to the present study. All other authors declare no biomedical financial interests or potential conflicts of interest.

Supplementary Results

Whole brain analyses

In the exploratory whole brain analysis in the reward-cognition interaction contrast across all subjects, we found significant activation in the right superior frontal gyrus (x = 17, y = 21, z = 58; k = 996, t = 6.13, FWEp < .01). Within the healthy control group, we did not find any significant activation. Within the patient group, we found significant activity in the right superior frontal gyrus (x = 22, y = 15, z = 56, k = 729, t = 7.21, FWEp < .01) and the middle occipital gyrus (x = -27, y = -89, z = 12, k = 2824, t = 6.51, FWEp < .05).

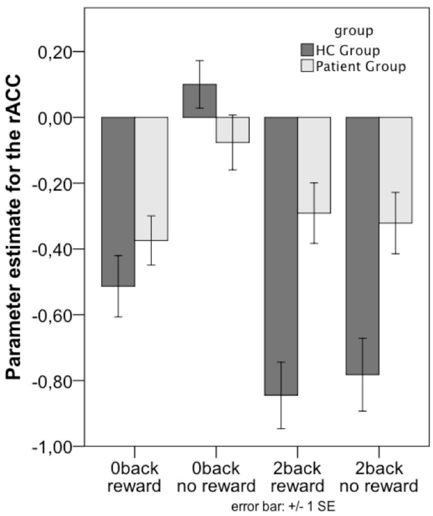
In the exploratory whole brain correlation analyses, we did not find any significant correlation of brain activity with negative symptoms.

Correlation analyses based on whole group interaction contrast

We extracted parameter estimates in the activated clusters in the whole group interaction contrast and calculated correlations with negative symptoms. As in our volume of interest analysis, we found a significant correlation of activity in the rACC with BNSS diminished expression, but not with BNSS apathy (see table below).

	rSFG [17,21,58]	**lSFG [-18,33,42]**	**rACC [9,44,1]**	**mSFG [8,68,18]**
BNSS Dim. Expr.	r = -.023 p = .906	r = -.057 p = .767	**r = -.434** **p = .019**	r = -.204 p = 289
BNSS Apathy	r = -.058 p = .767	r = .145 p = .452	r = .029 p = .880	r = -.030 p = .879

Supplementary Figure



Supplementary Figure. Mean parameter estimates of the activation in the rACC separate for both groups under all conditions.

Appendix C: Study 3

M. Kirschner, O. Hager, M. Bischof, M. Hartmann-Riemer, A. Kluge, E. Seifritz, P. Tobler, and S. Kaiser, accepted for publication. Deficits in Context-dependent Adaptive Coding of Reward in Schizophrenia. *npj Schizophrenia*

Appendix

Deficits in Context-dependent Adaptive Coding of Reward in Schizophrenia

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Word Count: Abstract: 249; Main text: 3779 (incl. Titles)
Number of figures: 5; Number of tables: 2

Abstract:

Background: A variety of impairments in reward-related processes in schizophrenia have been linked to deficits in the representation of rewards. However, it remains an open issue which neural mechanisms underlie these deficits. Theoretical principles of efficient information processing and empirical findings in single cells suggest that in order to efficiently represent all of the possible rewards, reward sensitive neurons adapt their coding range dynamically to the current reward context. A reduction in adaptive coding would affect the accurate representation of rewards and could potentially lie at the root of many dysfunctional reward processes in schizophrenia.

Methods: To investigate adaptive coding in patients with schizophrenia (n=27) and healthy controls (n=25), we used functional magnetic resonance imaging in combination with a variant of the monetary incentive delay task that involved two different reward contexts, allowing us to study adaptive coding of reward.

Results: Patients with schizophrenia did not efficiently adapt to the current reward context in two reward sensitive regions, the right caudate and the right anterior insula/inferior frontal gyrus. This inefficient adaptation led to diminished discriminability and, hence, imprecise neural representation particularly of small rewards. Importantly, general symptom severity was correlated with the deficit in reward coding adaptation.

Conclusion: Our results suggest that some of the deficits in reward representations in schizophrenia are linked to deficient adaptive coding of reward. Due to the ubiquity of adaptive coding in the brain, we believe that our findings provide an avenue to defining a general impairment in neural information processing underlying this disorder.

Key words: schizophrenia, functional magnetic resonance imaging, reward outcome, information-processing, dorsal striatum, anterior insula

1. Introduction

Aberrant reward processing is thought to play a major role in the pathophysiology of schizophrenia (1). Negative symptoms of schizophrenia have been associated with several processes linked to reward processing, such as impairments in reinforcement learning (2–8), reward anticipation (9–12) and cost-benefit computation (13–16). On the other hand, positive symptoms are discussed in terms of aberrant salience coding (17–24). All these processes require a precise representation of reward, which is crucial for optimal decision making and hence for efficient interaction with a dynamic environment (25; 26). Conversely, an imprecise representation of reward can potentially affect all reward-related processes that are impaired in patients with schizophrenia and could therefore characterize a core dysfunction related to the illness.

Reward is represented across several cortical and subcortical regions related to the dopaminergic system, such as the striatum, the orbitofrontal cortex, and the medial temporal cortices. Emerging evidence suggests that these representations are context specific, such that they adjust to the rewards that are available in the current context (25; 27–32). The dynamic adjustment in the firing of reward sensitive neurons to the current context is also known as adaptive coding of reward (33). This adaptation is necessary, because the coding range of any neuron, including reward-sensitive neurons, is limited (i.e. the firing rate can increase only up to some degree), whereas the diversity and range of potential inputs, including rewards, in our daily life is theoretically unlimited. Hence, if the full coding range would be devoted to represent all possible rewards, only relatively large differences in reward amounts could be represented and discrimination between amounts would be imprecise.

An efficient solution to this problem has been characterized both for sensory and reward systems. It consists of adapting the sensitivity of neurons to the range of (sensory or reward) inputs that are most probable in the current context. As a result, the slope of the response function of reward coding neurons is steeper in contexts with smaller reward ranges and shallower in contexts with larger reward ranges (see Figure 1A) (34). Thus, adapting slopes ensure optimal sensitivity to currently available rewards. This mechanism allows the organism to discriminate between different reward amounts as much as possible, and thereby enables informed decision making. On the other hand, if there is no adaptation, or if the adaptation is inefficient, reward information cannot be fully encoded, resulting in a loss of information and therefore in uncertainty about the precise reward amount of a stimulus or action (30). This uncertainty can be caused by two different mechanisms: In case the response function is too narrow, amounts at the extreme end of the distribution would be misrepresented. On the other hand, if the response function is too wide, it would result in unnecessarily flat slopes with poor discrimination between different amounts (see Figure 1B). In summary, a lack of dynamic neural adaptation leads to uncertainty in the representation of reward, which might result in detrimental decision making and a failure to efficiently engage with the environment.

Very little attention has been paid to the role of potential deficits in adaptive coding as a fundamental dysfunction of reward information processing in schizophrenia. To our knowledge, no study has investigated if dynamic neural adaptation to available rewards is deficient in schizophrenia. We therefore constructed a modified version of the monetary incentive delay task that enabled us to investigate adaptive coding of reward during the outcome phase. The findings for reward anticipation have been presented elsewhere (35).

We hypothesized that patients with schizophrenia show deficits in neural adaptation in reward coding regions, such as the striatum, in comparison to healthy controls. Furthermore, we were interested whether there is a correlation of the degree in adaptive reward coding with symptom severity in schizophrenia.

2. Methods and Materials

2.1 Participants

We included 29 patients with schizophrenia (SZ) and 28 healthy control participants (HC). Participants with SZ were recruited from outpatient (n = 12) and inpatient (n = 17) units of the Psychiatric Hospital of the University of Zurich or from affiliated institutions. All patients with SZ were clinically stable and received a stable dose of medication. The project was approved by the local ethics committee. All participants gave written informed consent to participate in the study. Diagnosis of schizophrenia was confirmed in a structured Mini-International Neuropsychiatric Interview for DSM-IV (36). We excluded participants with any other DSM-IV axis I disorder, medication with lorazepam higher than 1mg, acute psychotic symptoms, i.e. any positive subscale item score higher than four as measured with the Positive and Negative Syndrome Scale (PANSS) (37), and extrapyramidal side effects, i.e. a total score higher than two on the Modified Simpson-Angus Scale (MSAS) (38).

2.2 Clinical and Neuropsychological Assessment

All study participants underwent an extensive psychopathological assessment. Severity of positive and negative symptoms was assessed with the PANSS. Additionally, negative symptoms were specifically assessed with the brief negative symptom scale (BNSS) (39). Further psychopathological assessment included the Calgary Depression Scale for Schizophrenia (CDSS) (40), the Global Assessment of Functioning scale (GAF) (41), and the Personal and Social Performance Scale (PSP) (42). Moreover, both groups performed a neuropsychological test battery assessing verbal learning (Auditory Verbal Learning Memory Test) (43), verbal and visual short-term working memory [(digit span) (44) and (Corsi block-tapping test) (45)], processing speed (Digit-Symbol Coding) (46), planning (Tower of London) (47) and semantic and phonetic fluency (animal naming, s-words) (48). Results of all cognitive tests were summarized in a composite cognition score computed with the mean of z-transformed scores (based on HC group data). Additionally, we used the Multiple Word Test (49) to control for premorbid verbal intelligence.

2.3 Experimental Design and Task

We used a variant of the monetary incentive delay task (50) with stimuli based on the cued-reinforcement reaction time task used by Cools et al (51). This variant enabled us to investigate reward anticipation and reward outcome separately. In each correct trial (Figure 2), participants received a reward, which was determined directly by the individual response time. Thus, in contrast to most versions of the monetary incentive delay task, there was no dichotomy reward/no-reward in the outcome phase, but a continuous distribution of rewards. Importantly, our task included two different reward contexts, a low reward context, ranging from 0 to 0.4CHF, and a high reward context, ranging from 0 to 2CHF (in addition to a neutral control condition without reward). The differential reward range of the low and high reward context allowed us to investigate the dynamic adaptation of reward sensitive activation in the current reward context. In particular, adaptation would correspond to a steeper slope of the mapping between output (response strength) and input (reward amount) for the low reward context compared to the high reward context (Figure 1A and below).

Before starting the experiment, we informed all participants that they would receive the accumulated amount of money they won during the two experimental sessions. The maximum amount of money to be won was 50CHF. Every participant performed two training runs, one outside and one inside the scanner. Excluding the training sessions, the experiment contained two runs with 36 trials of about 10s each. The intertrial interval (ITI) was jittered from 1 to 9s with a mean of 3.5s. In total, one run lasted about 6min. The task was implemented using the MATLAB toolboxes Cogent 2000 and Cogent Graphics.

2.4 Functional Imaging Data Acquisition

Imaging data was collected with a Philips Achieva 3.0T magnetic resonance (MR) scanner using a 32 channel SENSE head coil (Philips, Best, The Netherlands) at the MR center at the Psychiatric Hospital, University of Zurich. Functional MRI (fMRI) was acquired in two runs with 195 ascending transverse plane images using a gradient-echo T2*-weighted echo-planar image (EPI) sequence over the whole brain. Acquired in-plane resolution was $3\times3mm^2$, 3mm slice thickness and 0.5mm gap width over a field of view of $240\times240mm^2$, a repetition/echo time (TR/TE) of 2000/25ms and a flip angle of 82°. The first five scans were discarded to eliminate the influence of T1 saturation effects. Slices were aligned with the anterior–posterior commissure. Anatomical data was acquired with an ultrafast gradient echo T1-weighted sequence in 160 sagittal plane slices of $240\times240mm^2$ resulting in $1x1x1mm^3$ voxels.

2.5 Data Analysis

All demographic, clinical, neuropsychological and behavioral data, as well as the correlations were analyzed using IBM SPSS Statistics Version 22. We analyzed fMRI data using SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK).

2.5.1 Behavioral Data

The main behavioral outcome measure was response time, defined as time between target presentation and pressing the correct answer button. We performed a two-way repeated measures analysis of variance (ANOVA) with group as between-subject factor and reward condition (low, high) as within-subject factor. Potential group differences in all other behavioral data were investigated using two sample t-tests. For non-normally distributed data (as assessed by the Kolmogorov-Smirnov test), Mann-Whitney U tests were applied.

2.5.2 Image Preprocessing

Functional images were corrected for differences in the time of slice acquisition. The Realign and Unwarp functions of SPM8 were used to correct our data for head motion. A voxel displacement map, calculated from double phase and magnitude field map data, was used to correct for combined static and dynamic distortions. We performed segmentation, bias correction, and spatial normalization. Finally, images were smoothed using a Gaussian kernel of 6 mm width at half maximum. We evaluated the quality of fMRI data by manual inspection and excluded data with poor quality due to significant signal dropout in EPI sequences (one patient with schizophrenia). Furthermore, participants with translational head movement >3mm (1 voxel size) were excluded (five participants, 3 HC, 2 SZ), leaving a total sample of 27 patients with schizophrenia and 25 healthy controls.

2.5.3 First Level Image Analyses

We computed a general linear model (GLM) with a parametric design to identify brain regions that encode reward in an adaptive fashion at the outcome phase. In particular, we modelled the onsets of each reward condition separately (no/low/high reward). Please note that these regressors accounted for potential differences in mean activation between the low (CHF 0.4) and the high reward condition (CHF 2.0). Importantly, the low and high reward outcome regressors were parametrically modulated (pmod) by the actual outcome won in each trial [pmod low reward, pmod high reward]. Thus, these modulators capture reward amount; pmod low ranged from CHF 0 to CHF 0.4, pmod high ranged from CHF 0.4 to CHF 2.0, resulting in a smaller range for the low reward outcomes. The anticipation phase for each condition, the target presentation for each condition and error trials were modeled as regressors of no interest. In total, the first level model included twelve regressors. The canonical hemodynamic response function was used for convolving all explanatory variables.

2.5.4 Second Level Image Analyses – Identification of reward coding regions

At the second level of analysis, we included the individual contrast images of all participants in a random-effects model. We assessed within-group activation using one sample t-tests and between-group activation using two sample t-tests. To identify reward coding brain regions, we used a contrast including both parametric modulators [pmod low + pmod high], which we applied in a voxel wise whole brain analysis across all participants. The statistical threshold was set to $p \leq .05$, whole-brain cluster-level family-wise error (FWE) rate corrected for multiple comparisons, with a cluster-inducing voxel threshold of $p < .001$.

2.5.5 Second Level Image Analyses – Adaptive coding of reward

In a second step, we tested adaptive coding of reward within the previously identified reward coding brain regions. Efficient neural adaptation of reward implies that the responses dynamically adjust to the range of possible rewards. Therefore, the slope of the response function should be steeper with a smaller reward range compared to a larger reward range (Figure 1A). Consequently, in case of adaptive coding in our task, the slope of the response function in the low reward condition should be steeper than the slope in the high reward condition. To test for a significant difference, we therefore subtracted the parametric regressor of the high reward from the low reward condition [pmod low reward – pmod high reward]. A significant result provides strong evidence for adaptive coding, because it reflects significant differences in the slope of the reward response function.

According to our primary hypothesis, we tested if patients with schizophrenia show deficits in context-dependent neural adaptation compared to healthy controls. Therefore, we computed group differences between healthy controls and patients with schizophrenia in the adaptive coding contrast [(HC (pmod low reward) – (pmod high reward)) - (SZ (pmod low reward) – (pmod high reward))]. Please note that this contrast is independent of the one used to identify the reward-related ROIs. Finally, we evaluated if efficient adaptation of reward is correlated with symptom severity in patients with schizophrenia. Therefore, we performed bivariate Pearson correlation analyses between the adaptive coding contrast estimate [(pmod low reward) – (pmod high reward)] and symptom severity ratings.

3. Results

3.1 Sample Characteristics
Participant demographics, clinical data and group comparisons are summarized in Table 1.

3.2 Behavioral Data
Regarding response time, the repeated measures ANOVA revealed no significant main effect of group [$F(1, 50)=2.91$, $p=.09$], but a significant main effect of reward condition [$F(1, 50)=36.2$, $p<.0001$]. Across all participants, response times were faster in the high reward condition, indicating that participants adapted their behavior to the different reward context (low vs. high reward). There was no significant group by reward interaction effect [$F(1,50)=.65$, $p=.47$]. Due to low error rates we used a total error score for group comparison and did not find any group differences (HC=3.3 (2.5); SZ=3.8 (2.8.); $U=315$, $p=.68$). Finally, both groups differed significantly in total win (HC=38.9 (5.2); SZ=36 (4.6); $t=2.1$, $p=.04$), although the differences were small.

3.3 fMRI Data

3.3.1 Brain regions coding reward
Voxel-wise whole brain analysis across all subjects during reward outcome [pmod low reward + pmod high reward] revealed several brain regions coding for reward (cluster-level FWE-corrected, $p \leq .05$), i.e. the ventral and dorsal striatum, medial orbitofrontal cortex and anterior insula/inferior frontal gyrus (see Table 2). Thus, activation in these regions increases with reward amount at the time of outcome.

3.3.2 Group differences in adaptive coding of reward
Within these reward sensitive regions, we tested for group differences in adaptive coding between healthy controls and patients with SZ. Specifically, we compared the slope differences in the reward response functions for low and high reward [(HC (pmod low reward) – (pmod high reward)) - (SZ (pmod low reward) – (pmod high reward))]. In the dorsal striatum (x=21, y=3, z=22; cluster size=19, $t=4.7$, FWE corrected $p \leq .05$, Figure 3A) and the anterior insula/inferior frontal gyrus (x=50, y=-4, z=6; cluster size=24, $t=5.43$, FWE corrected $p \leq .05$, Figure 3B), healthy controls showed significantly stronger adaptive coding [pmod low reward – pmod high reward] relative to patients with schizophrenia. Additionally, results were similar when we used an anatomically defined ROI of the striatum defined with the wfu pickatlas SPM8 (right: x=23, y=2, z=21, cluster size=39; left: x=-6, y=14, z=12, cluster size=8, both FWE corrected $p \leq .05$). These findings imply significant differences between the slope of the response function in the low reward and high reward condition in healthy controls, but not in patients with schizophrenia. In other words, these significant group differences provide strong evidence for efficient neural adaptation of reward coding in the dorsal striatum and anterior insula/inferior frontal gyrus in healthy controls, but not in the patient group. To

visualize these differences in the adaptive coding of reward, we plotted the response functions of the neural activity in the low and high reward condition separately (Figure 4).

Next, we tested whether there are any clusters in the reward sensitive regions where patients with schizophrenia show more efficient adaptive coding of reward than healthy controls [(SZ (pmod low reward) – pmod high reward)) – (HC (pmod low reward) – (pmod high reward))]. In this analysis we did not find any significant activation at the previously used more stringent threshold (FWE corrected, $p \leq .05$) and only one single voxel at a more lenient threshold ($p < .001$, uncorrected).

3.4 Correlation Analysis

Correlation analysis between adaptive coding contrast estimates [(pmod low reward) – (pmod high reward)] in the right caudate and symptom severity rated with the PANSS total score ($r=-.56$, $p<.01$) revealed a highly significant negative correlation in the patient group (Figure 5). Importantly, this effect was also present for positive symptoms (PANSS positive symptom score; $r=-50$, $p<.01$), negative symptoms (PANSS negative symptom score; $r=-.45$, $p=.02$) and general symptoms (PANSS general symptom score; $r=-.47$, $p=.01$). Furthermore, we found a trend effect with the BNSS total score ($r=-.37$, $p=.06$) in the patient group. There were no significant correlations with the two negative symptom factors apathy ($r=-.30$, $p=.12$) and diminished expression ($r=-.32$, $p=.10$). Potential confounding variables such as chlorpromazine equivalents ($r=-.04$, $p=.85$) or cognition (composite cognition score; $r=-.13$, $p=.51$) showed no significant association with deficient adaptive coding of reward. In sum, higher symptom severity was associated with less adaptive coding in the caudate.

The correlation analysis between adaptive coding contrast estimates [(pmod low reward) – (pmod high reward)] in the anterior insula/inferior gyrus and symptom severity, measured with the PANSS total score yielded a negative trend level correlation ($r=-.34$, $p=.08$) and no significant correlation with the BNSS ($r=-.05$, $p=.80$).

4. Discussion

In the current study, we used a modified version of the monetary incentive delay paradigm to investigate adaptive reward coding for the first time in patients with schizophrenia. We found that patients with schizophrenia show inefficient adaptive coding in two reward sensitive regions, namely in the right caudate and the right anterior insula/inferior frontal gyrus. These findings imply that patients with schizophrenia are not able to precisely represent reward information within these two regions due to a failure to adjust neural sensitivity to the available rewards. Furthermore, we could show that the deficit in adaptive coding is related to the total symptom severity of patients with schizophrenia. This was the case particularly for the right caudate, where we found a significant negative correlation of the adaptive coding deficits with the PANSS total score and with the PANSS subscales. Overall, these findings suggest that patients with schizophrenia have deficits in adaptive coding of rewards due to a diminished discriminability of different reward amounts. This decreased sensitivity leads to an imprecise representation of reward information.

The significant deficits in adaptive coding of patients diagnosed with schizophrenia relative to healthy controls were found in two reward sensitive regions - the right caudate and the right

AI/IFG. In the right caudate, patients only exploit a fraction of the response range to represent reward information compared to healthy controls, which impairs discriminability between different reward amounts. The caudate, together with the putamen, forms the dorsal part of the striatum, which is involved in learning about actions and their reward consequences as well as the selection of actions based on the reward they are associated with (52–55). Our findings of an adaptive coding deficit is in line with work by Morris and colleagues (56) who recently described an association of caudate dysfunction with an impairment in integrating changes in experienced reward values (devaluation of food rewards) to guide choice behavior in patients with schizophrenia.

In the AI/IFG, adaptive coding in the low reward condition was so disrupted in patients that reward amount was no longer encoded with a positive slope. However, reward amount in the high reward condition was encoded similarly to healthy controls, suggesting partly preserved sensitivity to reward. The observed deficits in adaptive coding in the anterior insula and the related structure of the IFG are in line with aberrant salience processing observed in schizophrenia (57–60). Specifically, the imprecise neural representation of reward information could lead to increased uncertainty about external stimuli or internal values, which in turn may alter the processing of what is important. In support of this notion, Anselme and colleagues recently reported that reward uncertainty enhances salience attribution (61).

We found that patients with schizophrenia show poorer neural discrimination of different rewards. This inefficient adaptation results in an imprecise encoding of reward information, which has potentially far-reaching consequences. It can affect all reward related processes and hence severely impinge on an organism's ability to optimally interact with its environment. Several studies have already reported that patients with schizophrenia have difficulties in reward representations. Gold et al. (3) found a correlation of negative symptoms with a deficit in learning from rewarding outcomes. They suggested that this deficit is related to impairment in the representation of value. Gold et al. (14) and Hartmann et al. (15) both report that impairments in effort based decision making in schizophrenia might be related to alterations in value representations. For the first time, we could show that deficits in reward representation can result from an inefficient adaptation of neural sensitivity to the current reward context.

Our findings expand the current understanding of reward processing deficits in schizophrenia substantially by introducing a new concept – the contextual adaptation of neural sensitivity to reward. Furthermore, we could show that the deficit in adaptive coding is related to total symptom severity. This suggests that the deficit in adaptive coding of reward could reflect a more basic dysfunction instead of a specific neural correlate of positive, negative, or depressive symptoms (1; 62–64). Here, it is important to consider that context-dependent adaptation of neural activity does not solely apply to the encoding of reward information, but also to sensory information processing, i.e., the processing of auditory and visual information (65; 66). Although speculative, such a general deficit in context-dependent adaptation might contribute to a better understanding of deficits in sensory information-processing observed in patients with schizophrenia (24; 67; 68). Furthermore, earlier studies have proposed that the "core" cognitive deficit in schizophrenia is a disturbance of context information processing (69–71). However, to support this hypothesis of a general underlying deficit, further studies elucidating context-dependent neural adaptation in other domains, such as sensory and cognitive information processing, are needed.

Some limitations of this study are worth mentioning. Although in our analysis, we did not find any statistical effect of antipsychotic medication, we cannot fully exclude potential confounding effects due to atypical antipsychotics. Therefore, it would be important to investigate whether our findings can be generalized to antipsychotic naïve patients and patients with first generation antipsychotics. Furthermore, our sample showed relatively low levels of positive and depressive symptoms, which limits the possibility to differentiate specific effects of these domains. Thus, further research is needed to clarify whether the impairment in adaptive coding is indeed a general disturbance associated with schizophrenia. Lastly, it has to be mentioned that due to the task design, it is difficult to precisely disentangle whether the observed changes in adaptive outcome coding reflect disturbances in the processing of experienced reward or of a reward prediction error (i.e. the difference between predicted and experienced reward).

In summary, the present findings provide the first evidence that patients with schizophrenia show inefficient adaptive coding of reward. This deficit causes an imprecise representation of reward information due to diminished discriminability of different reward amounts. At a behavioral level, this basic information-processing deficit may be partly responsible for impaired reinforcement learning, deficits in cost-benefit computations and aberrant salience coding. This broad potential impact on reward-related processes would be in line with the observation that the adaptive coding deficit is related to total symptom severity. We believe that this finding not only contributes to a better understanding of the reward processing deficits in schizophrenia, but – due to the ubiquity of this process – suggests an approach to identify a general impairment in neural mechanisms underlying this debilitating disorder.

5. References

1. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA (2008): Reward Processing in Schizophrenia: A Deficit in the Representation of Value. *Schizophr Bull*. 34: 835–847.

2. Deserno L, Boehme R, Heinz A, Schlagenhauf F (2013): Reinforcement Learning and Dopamine in Schizophrenia: Dimensions of Symptoms or Specific Features of a Disease Group? *Front Psychiatry*. 4. doi: 10.3389/fpsyt.2013.00172.

3. Gold JM, Waltz JA, Matveeva TM, et al (2012): Negative symptoms and the failure to represent the expected reward value of actions: Behavioral and computational modeling evidence. *Arch Gen Psychiatry*. 69: 129–138.

4. Strauss GP, Frank MJ, Waltz JA, Kasanova Z, Herbener ES, Gold JM (2011): Deficits in Positive Reinforcement Learning and Uncertainty-Driven Exploration Are Associated with Distinct Aspects of Negative Symptoms in Schizophrenia. *Biol Psychiatry*, Schizophrenia: From Circuit Dysfunction to Treatment? 69: 424–431.

5. Waltz JA, Gold JM (2007): Probabilistic reversal learning impairments in schizophrenia: Further evidence of orbitofrontal dysfunction. *Schizophr Res*. 93: 296–303.

6. Waltz JA, Schweitzer JB, Gold JM, Kurup PK, Ross TJ, Jo Salmeron B, *et al.* (2008): Patients with Schizophrenia have a Reduced Neural Response to Both Unpredictable and Predictable Primary Reinforcers. *Neuropsychopharmacology*. 34: 1567–1577.

7. Murray GK, Cheng F, Clark L, Barnett JH, Blackwell AD, Fletcher PC, *et al.* (2008): Reinforcement and reversal learning in first-episode psychosis. *Schizophr Bull*. 34: 848–855.

8. Waltz JA, Frank MJ, Robinson BM, Gold JM (2007): Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biol Psychiatry*. 62: 756–764.

9. Mucci A, Dima D, Soricelli A, Volpe U, Bucci P, Frangou S, *et al.* (2015): Is avolition in schizophrenia associated with a deficit of dorsal caudate activity? A functional magnetic resonance imaging study during reward anticipation and feedback. *Psychol Med*. 1–14.

10. Waltz JA, Schweitzer JB, Ross TJ, Kurup PK, Salmeron BJ, Rose EJ, *et al.* (2011): Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. *Neuropsychopharmacology*. 35: 2427–39.

11. Simon JJ, Biller A, Walther S, Roesch-Ely D, Stippich C, Weisbrod M, Kaiser S (2010): Neural correlates of reward processing in schizophrenia--relationship to apathy and depression. *Schizophr Res*. 118: 154–61.

12. Morris RW, Vercammen A, Lenroot R, Moore L, Langton JM, Short B, *et al.* (2012): Disambiguating ventral striatum fMRI-related bold signal during reward prediction in schizophrenia. *Mol Psychiatry*. 17: 280–289.

13. Fervaha G, Graff-Guerrero A, Zakzanis KK, Foussias G, Agid O, Remington G (2013): Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making. *J Psychiatr Res*. 47: 1590–1596.

14. Gold JM, Strauss GP, Waltz JA, Robinson BM, Brown JK, Frank MJ (2013): Negative Symptoms of Schizophrenia Are Associated with Abnormal Effort-Cost Computations. *Biol Psychiatry*, Corticostriatal Networks, Psychopathology, and Treatment. 74: 130–136.

15. Hartmann MN, Hager OM, Reimann AV, Chumbley JR, Kirschner M, Seifritz E, *et al.* (2014): Apathy But Not Diminished Expression in Schizophrenia Is Associated With Discounting of Monetary Rewards by Physical Effort. *Schizophr Bull*. sbu102.

16. Treadway MT, Bossaller N, Shelton RC, Zald DH (2012): Effort-Based Decision-Making in Major Depressive Disorder: A Translational Model of Motivational Anhedonia. *J Abnorm Psychol*. 121: 553–558.

17. Nielsen MØ, Rostrup E, Wulff S, Bak N, Lublin H, Kapur S, Glenthøj B (2012): Alterations of the Brain Reward System in Antipsychotic Naïve Schizophrenia Patients. *Biol Psychiatry*, Altered Functional Connectivity in Schizophrenia. 71: 898–905.

18. Schlagenhauf F, Sterzer P, Schmack K, Ballmaier M, Rapp M, Wrase J, *et al.* (2009): Reward Feedback Alterations in Unmedicated Schizophrenia Patients: Relevance for Delusions. *Biol Psychiatry*, The Interplay of GABA, Glutamate, and Dopamine in Schizophrenia and Its Treatment. 65: 1032–1039.

19. Walter H, Kammerer H, Frasch K, Spitzer M, Abler B (2009): Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. *Psychopharmacology (Berl)*. 206: 121–132.

20. Corlett PR, Murray GK, Honey GD, Aitken MRF, Shanks DR, Robbins TW, *et al.* (2007): Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain*. 130: 2387–2400.

21. Morris R, Griffiths O, Pelley MEL, Weickert TW (2013): Attention to Irrelevant Cues Is Related to Positive Symptoms in Schizophrenia. *Schizophr Bull*. 39: 575–582.

22. Corlett PR, Simons JS, Pigott JS, Gardner JM, Murray GK, Krystal JH, Fletcher PC (2009): Illusions and delusions: relating experimentally-induced false memories to anomalous experiences and ideas. *Front Behav Neurosci*. 3: 53.

23. Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, *et al.* (2008): Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol Psychiatry*. 13: 239, 267–276.

24. Kiehl KA, Stevens MC, Celone K, Kurtz M, Krystal JH (2005): Abnormal hemodynamics in schizophrenia during an auditory oddball task. *Biol Psychiatry*. 57: 1029–1040.

25. Cox KM, Kable JW (2014): BOLD Subjective Value Signals Exhibit Robust Range Adaptation. *J Neurosci*. 34: 16533–16543.

26. Park SQ, Kahnt T, Talmi D, Rieskamp J, Dolan RJ, Heekeren HR (2012): Adaptive coding of reward prediction errors is gated by striatal coupling. *Proc Natl Acad Sci*. 109: 4285–4289.

27. Breiter HC, Aharon I, Kahneman D, Dale A, Shizgal P (2001): Functional Imaging of Neural Responses to Expectancy and Experience of Monetary Gains and Losses. *Neuron*. 30: 619–639.

28. Bunzeck N, Düzel E (2006): Absolute Coding of Stimulus Novelty in the Human Substantia Nigra/VTA. *Neuron*. 51: 369–379.

29. Elliott R, Agnew Z, Deakin JFW (2008): Medial orbitofrontal cortex codes relative rather than absolute value of financial rewards in humans. *Eur J Neurosci*. 27: 2213–2218.

30. Kobayashi S, Carvalho OP de, Schultz W (2010): Adaptation of Reward Sensitivity in Orbitofrontal Neurons. *J Neurosci*. 30: 534–544.

31. Nieuwenhuis S, Heslenfeld DJ, Alting von Geusau NJ, Mars RB, Holroyd CB, Yeung N (2005): Activity in human reward-sensitive brain areas is strongly context dependent. *NeuroImage*. 25: 1302–1309.

32. Padoa-Schioppa C (2009): Range-Adapting Representation of Economic Value in the Orbitofrontal Cortex. *J Neurosci*. 29: 14004–14014.

33. Tobler PN, Fiorillo CD, Schultz W (2005): Adaptive Coding of Reward Value by Dopamine Neurons. *Science*. 307: 1642–1645.

34. Louie K, Glimcher PW (2012): Efficient coding and the neural representation of value. *Ann N Y Acad Sci*. 1251: 13–32.

35. Kirschner M, Hager O, Hartmann M, Kluge A, Bischof M, Seifritz E, *et al.* (2015): Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia. *J Psychiatry Neurosci JPN*. in press.

36. Lecrubier Y, Weiller E, Herugeta T, Amorim P, Bonora LI, Lépine JP, *et al.* (1999): *Mini International Neurpsychiatric Interview German Version 5.0.0*. München: Psychiatrischen Universitätsklinik München.

37. Kay SR, Opler LA, Lindenmayer JP (1989): The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. *Br J Psychiatry Suppl*. 59–67.

38. Simpson GM, Angus JW (1970): A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl*. 212: 11–9.

39. Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, Marder SR (2011): The brief negative symptom scale: psychometric properties. *Schizophr Bull*. 37: 300–5.

40. Addington D, Addington J, Schissel B (1990): A depression rating scale for schizophrenics. *Schizophr Res*. 3: 247–51.

41. Frances A, Pincus HA, First MB (1994): The Global Assessment of Functioning Scale (GAF). Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.

42. Juckel G, Schaub D, Fuchs N, Naumann U, Uhl I, Witthaus H, *et al.* (2008): Validation of the Personal and Social Performance (PSP) Scale in a German sample of acutely ill patients with schizophrenia. *Schizophr Res*. 104: 287–293.

43. Helmstaedter C, Lendt M, Lux S. (2001): VLMT. Verbaler Lern- und Merkfähigkeitstest. .

44. Härting C, Markowitsch HJ, Neufeld H (2000): Wechsler Memory Scale - Revised Edition, German Edition. Manual. Bern, Switzerland: Huber.

45. Kessels RP, van Zandvoort MJ, Postma A, Kappelle LJ, de Haan EH (2000): The Corsi Block-Tapping Task: standardization and normative data. *Appl Neuropsychol*. 7: 252–258.

46. Von Aster M, Neubauer A, Horn R. (n.d.): *Wechsler Intelligenztest für Erwachsene WIE. Deutschsprachige Bearbeitung und Adaption des WAIS-III von David Wechsler*. Frankfurt, Germany: Pearson Assessment; 2006.

47. Shallice T (1982): Specific impairments of planning. *Philos Trans R Soc Lond B Biol Sci*. 298: 199–209.

48. Delis DC, Kaplan E, Kramer J. (2001): *Delis Kaplan Executive Function System*. San Antonio, TX: The Psychological Corporation; 2001.

49. Lehrl S, Triebig G, Fischer B (1995): Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol Scand*. 91: 335–345.

50. Knutson B, Westdorp A, Kaiser E, Hommer D (2000): FMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage*. 12: 20–27.

51. Cools R, Blackwell A, Clark L, Menzies L, Cox S, Robbins TW (2005): Tryptophan depletion disrupts the motivational guidance of goal-directed behavior as a function of trait impulsivity. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 30: 1362–1373.

52. Balleine BW, Delgado MR, Hikosaka O (2007): The Role of the Dorsal Striatum in Reward and Decision-Making. *J Neurosci*. 27: 8161–8165.

53. Grahn JA, Parkinson JA, Owen AM (2008): The cognitive functions of the caudate nucleus. *Prog Neurobiol*. 86: 141–155.

54. Hikosaka O, Kim HF, Yasuda M, Yamamoto S (2014): Basal ganglia circuits for reward value-guided behavior. *Annu Rev Neurosci*. 37: 289–306.

55. Wickens JR, Budd CS, Hyland BI, Arbuthnott GW (2007): Striatal Contributions to Reward and Decision Making. *Ann N Y Acad Sci*. 1104: 192–212.

56. Morris RW, Quail S, Griffiths KR, Green MJ, Balleine BW (2015): Corticostriatal Control of Goal-Directed Action Is Impaired in Schizophrenia. *Biol Psychiatry*, Schizophrenia and Neurodevelopment. 77: 187–195.

57. Kapur S (2003): Psychosis as a State of Aberrant Salience: A Framework Linking Biology, Phenomenology, and Pharmacology in Schizophrenia. *Am J Psychiatry*. 160: 13–23.

58. Smieskova R, Roiser JP, Chaddock CA, Schmidt A, Harrisberger F, Bendfeldt K, *et al.* (n.d.): Modulation of motivational salience processing during the early stages of psychosis. *Schizophr Res*. . doi: 10.1016/j.schres.2015.04.036.

59. Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, *et al.* (2007): Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *J Neurosci*. 27: 2349–2356.

60. Dosenbach NUF, Fair DA, Miezin FM, Cohen AL, Wenger KK, Dosenbach RAT, *et al.* (2007): Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci*. 104: 11073–11078.

61. Anselme P, Robinson MJF, Berridge KC (2013): Reward uncertainty enhances incentive salience attribution as sign-tracking. *Behav Brain Res*. 238: 53–61.

62. Griffiths KR, Morris RW, Balleine BW (2014): Translational studies of goal-directed action as a framework for classifying deficits across psychiatric disorders. *Front Syst Neurosci*. 8. doi: 10.3389/fnsys.2014.00101.

63. Heerey EA, Bell-Warren KR, Gold JM (2008): Decision-Making Impairments in the Context of Intact Reward Sensitivity in Schizophrenia. *Biol Psychiatry*, Cognitive Neuroscience Approaches to Treatment Development of Impaired Cognition in Schizophrenia: Proceedings of the First Meeting of the CNTRICS Initiative. 64: 62–69.

64. Heerey EA, Gold JM (2007): Patients with schizophrenia demonstrate dissociation between affective experience and motivated behavior. *J Abnorm Psychol*. 116: 268–278.

65. Smith EC, Lewicki MS (2006): Efficient auditory coding. *Nature*. 439: 978–982.

66. Wark B, Lundstrom BN, Fairhall A (2007): Sensory adaptation. *Curr Opin Neurobiol*, Sensory systems. 17: 423–429.

67. Javitt DC, Doneshka P, Zylberman I, Ritter W, Vaughan Jr. HG (1993): Impairment of early cortical processing in schizophrenia: An event-related potential confirmation study. *Biol Psychiatry*. 33: 513–519.

68. Turetsky BI, Bilker WB, Siegel SJ, Kohler CG, Gur RE (2009): Profile of auditory information-processing deficits in schizophrenia. *Psychiatry Res*. 165: 27–37.

69. Barch DM, Carter CS, Braver TS, et al (2001): SElective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. *Arch Gen Psychiatry*. 58: 280–288.

70. Cohen JD, Servan-Schreiber D (1992): Context, cortex, and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychol Rev*. 99: 45–77.

71. Hemsley DR (2005): The Schizophrenic Experience: Taken Out of Context? *Schizophr Bull*. 31: 43–53.

Tables

Table 1

	Patient Group (n = 27)	Healthy Controls (n = 25)	Test Statistic ($t/X^2/U$)	P
Age	31.9 (7.1)	33.0 (9.7)	U = 322.00	.78
Gender (female/male)	9/18	9/16	X^2 = .04	.81
Education in years	12.2 (3.0)	12.4 (3.6)	U = 334.00	.95
Duration of illness in years	9.2 (6.6)	–	–	–
Age of onset in years	22.7 (6)	–	–	–
Chlorpromazine equivalents (mg/d)	491.3 (349.5)	–	–	–
Psychopathology				
PANSS positive	11.2 (2.9)	–	–	–
PANSS negative	14.7 (5.8)	–	–	–
PANSS general psychopathology	23.5 (4.8)	–	–	–
PANSS total	49.4 (11.2)	–	–	–
BNSS apathy[a]	14.8 (6.9)	–	–	–
BNSS diminished expression[b]	8.5 (7.2)	–	–	–
BNSS total	24.6 (12.4)	–	–	–
CDSS Total	1.6 (2.2)	–	–	–
GAF	56.9 (9.6)	–	–	–
PSP Total	56.4 (9.9)	–	–	–
Cognition[c]				
Composite cognition score	-.62 (.89)	0 (.53)	t = 3.0	**.01**
MWT IQ	25.9 (5.8)	27.6 (4.0)	t = 1.2	.23

Note: Data are presented as means and standard deviations. Potential group differences were investigated using 2-sample *t* tests for continuous and chi-square tests for categorical data. For non-normally distributed data Mann-Whitney *U* tests were applied. All patients were receiving atypical antipsychotics at the time of testing. PANSS, Positive and Negative Syndrome Scale; BNSS, Brief Negative Symptom Scale; SANS, Scale for the Assessment of Negative Symptoms; CDSS, Calgary Depression Scale for Schizophrenia; GAF, Global Assessment of Functioning; PSP, Personal and Social Performance Scale; MWT IQ, Multiple Word Test Intelligence Quotient.

[a] Apathy = Avolition, Anhedonia, Asociality; [b] Diminished Expression = Affective Flattening or Blunting, Alogia.

[c] Cognition data were z-transformed based on the data of the HC group for each test separately. The Composite cognition score was computed as the mean of the z-transformed test scores on subject level.

Table 2

	X	Y	Z	Cluster Size	t
Middle frontal gyrus	**-24**	**24**	**52**	**1780**	**6.29**
	-17	18	61		5.44
	-22	43	25		5.43
Inferior parietal lobe	**-46**	**-63**	**40**	**7494**	**6.29**
	16	-88	25		6.07
	6	-75	24		5.70
Dorsal Striatum	**25**	**-31**	**28**	**3062**	**6.07**
	30	-18	28.5		5.35
	16	-33	69		5.33
Insula/ inferior frontal gyrus	**60**	**3**	**12**	**657**	**5.84**
	31	-6	3		5.80
	39	-4	10		4.38
Putamen left	**-21**	**6**	**-10**	**1300**	**5.5**
	-9	24	-16		5.1
	-23	12	-2		5.0
Putamen right	**23**	**6**	**-10**	**685**	**5.4**
	8	23	-11		4.5
	14	21	-2		4.3
mOFC	**-8**	**54**	**-6**	**267**	**5.0**
	-3	62	1		4.2
Postcentral gyrus left	**-26**	**-36**	**73**	**781**	**4.8**
	-24	-28	54		4.4
	-22	-30	67		4.4
Paracentral gyrus	**5**	**-31**	**61**	**830**	**4.7**
	-2	-43	60		4.4
	-6	-40	51		4.3

Whole brain analysis of the contrast reward outcome [pmodLow + pmodHigh Reward], family wise error corrected (FWE) p<.05, across all subjects.

Figures

Figure 1

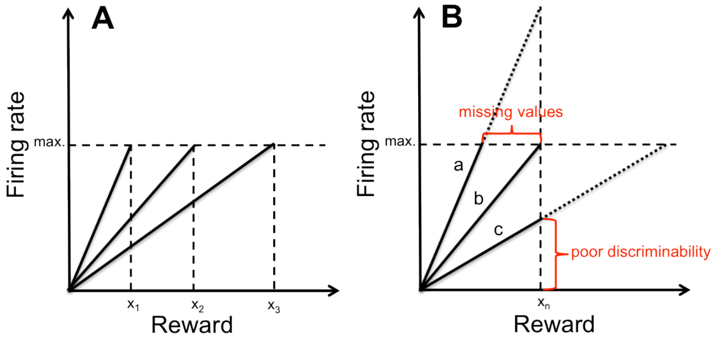

Figure Legend:
A) A simple model of adaptive coding of reward. To efficiently encode all possible rewards with a limited coding range, the brain is dynamically adjusting the response sensitivity to the currently available rewards. This mechanism allows to optimally discriminate between different amounts of reward in any given context, enabling efficient processing of reward information. B) Contrast of optimal and disturbed adaptive coding. This plot illustrates two potential consequences of inefficient adaptation of the coding range. Response function a) is too steep, leading to a miscoding/incomplete representation of reward information. Response function c) is too shallow, which leads to poor discriminability of reward due to a restricted coding range. Response function b) shows optimal adaptive reward coding, where the slope of the response function adapts so as to represent the full range of reward.

Figure 2

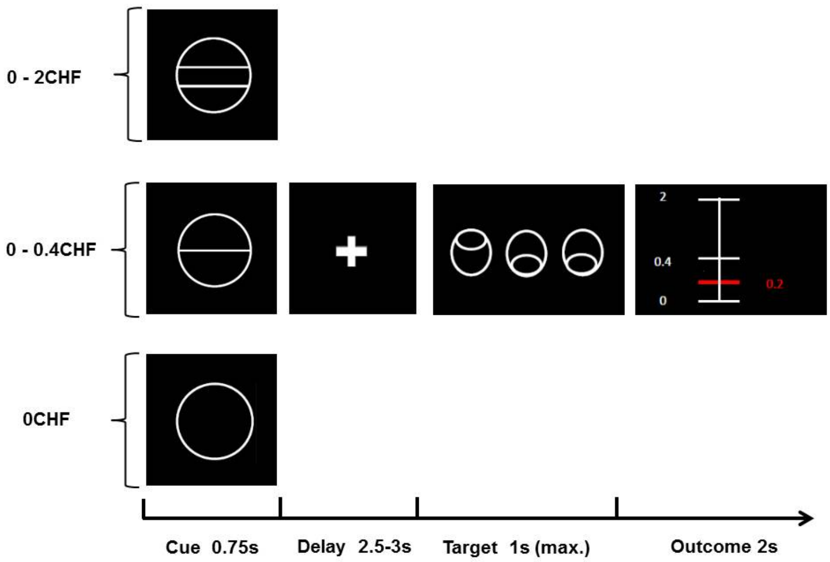

Figure Legend:

Adapted monetary incentive delay task: At the beginning of each trial, one of three different cues was presented for 0.75s. The cue indicated the reward context, specifically the range of possible amounts participants could gain in that trial, i.e. 0 to 2 Swiss Francs (CHF) (circle with two lines), 0 to 0.40CHF (circle with one line), or 0CHF (circle only) (1CHF = 1.08US $). After a delay, varying from 2.5 to 3s, the participants had to identify an outlier from three presented circles and press a button (either left or right) as fast as possible (varying from 0.32 to 1s). In case of a correct answer, participants were immediately notified of the amount of money they had won, which directly depended on their individual task performance (duration of feedback 2s). The gain of each trial was calculated based on the response times of the previous 15 individual trials. Error trials were defined as trials with a wrong response or late response (after 1s) and participants did not receive any monetary reward.

Figure 3

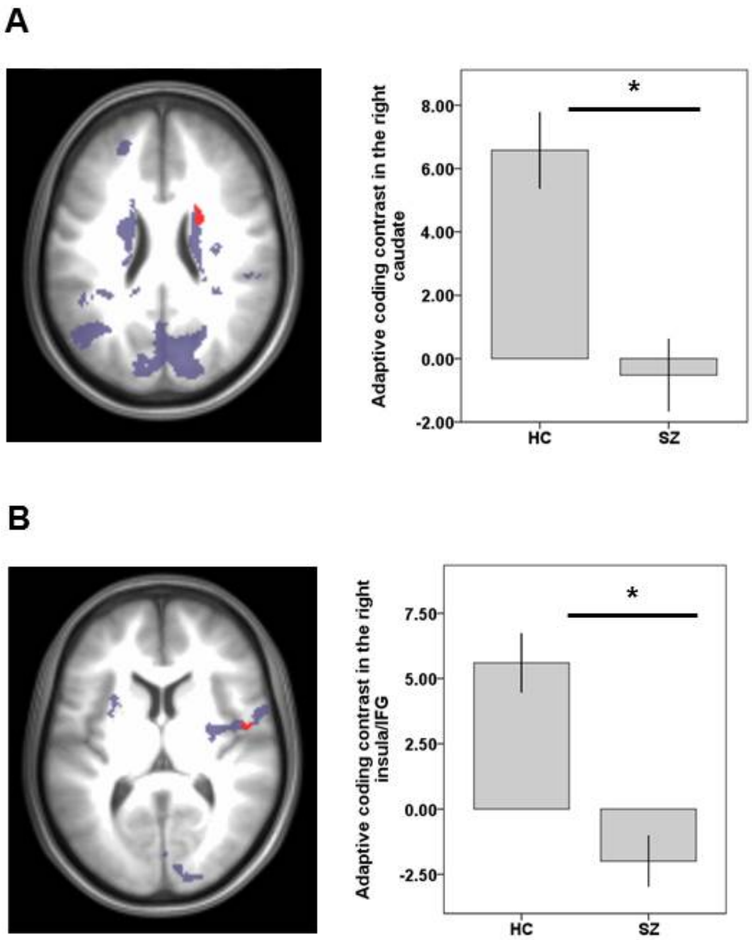

Figure Legend:

Brain regions responding to reward amount and showing differential adaptive coding. Reward responses [(pmod low reward) + (pmod high reward)] are colored in blue. Colored in red are clusters where healthy controls showed significantly stronger activation increases in the adaptive coding contrast [(pmod low reward) – (pmod high reward)]. Brain images thresholded at p<.05 (FWE). (A) Axial image in the right caudate. (B) Axial image of the right insula/IFG. Columns in bar graphs illustrate red clusters and reflect adaptive coding contrast estimates [(pmod low reward) – (pmod high reward)] for each group separately.

Figure 4

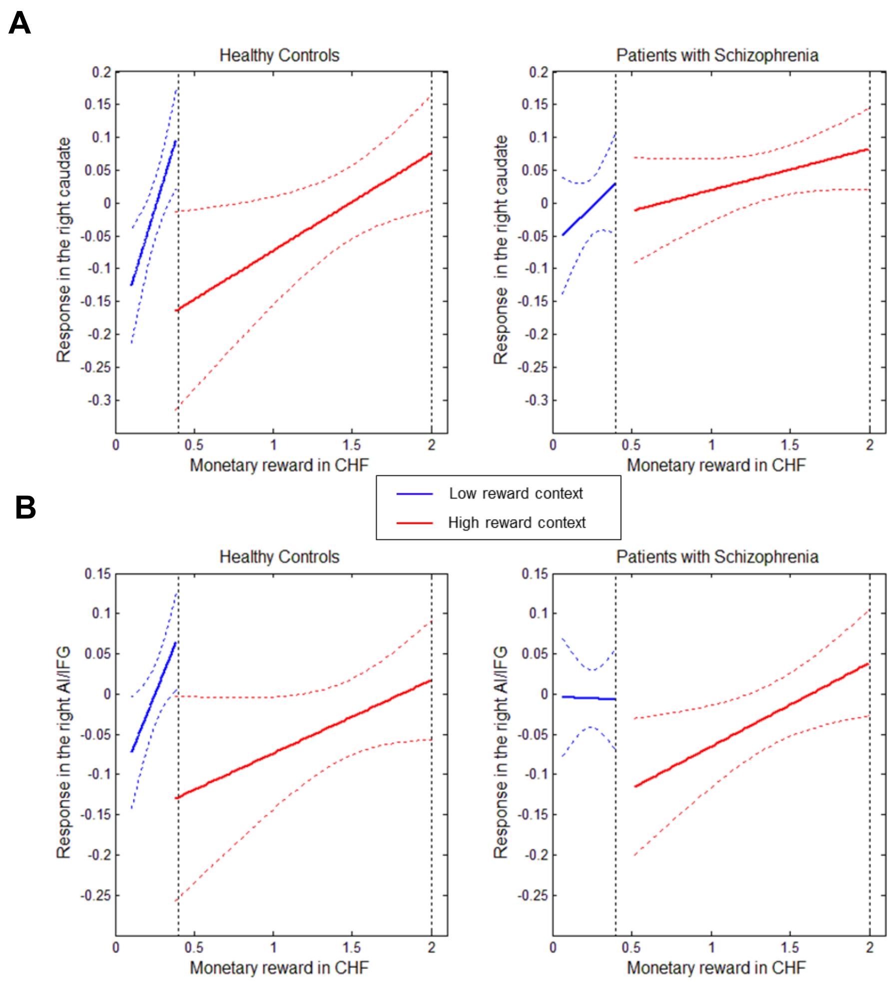

Figure Legend:

Response functions in the right caudate (Figure 4A) and the right anterior insula/inferior frontal gyrus (Figure 4B) plotted separately for the low reward (blue) and the high reward (red) context. Healthy controls optimally adapt the coding range to the current range of rewards in both regions, resulting in a steeper slope of neural responses in the low reward context than in the high reward context (figures 4A and 4B left). In contrast, patients with schizophrenia show significant deficits in adaptive coding, with insufficient slope increase (caudate; figure 4A right) or even shallower slope (insula; figure 4B right) for the low reward context compared to the high reward context. The diminished steepness of slopes translates to reduced discriminability in both reward contexts for the right caudate of patients. By contrast, in the right AI/IFG, discriminability was reduced primarily in the low reward context, whereas it was comparable to the discriminability of healthy controls in the high reward context.

Figure 5

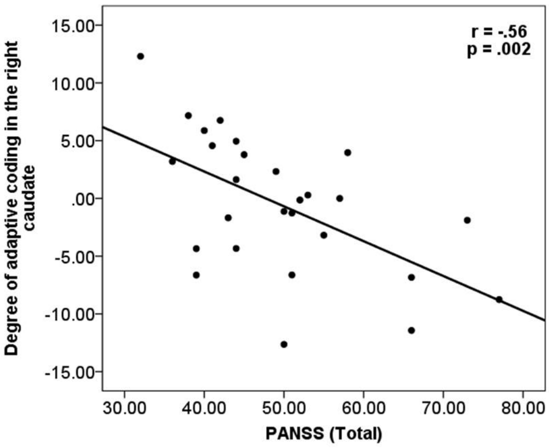

Figure Legend:
Correlation plots of the adaptive coding contrast estimates with the PANSS total score in patients with schizophrenia. In the right caudate, we found a significant negative correlation of the degree of adaptive coding with the PANSS total score.

Acknowledgments
This study was supported by the Swiss National Science Foundation (Grant No. 105314_140351 to Stefan Kaiser). Philippe N Tobler was supported by the Swiss National Science Foundation (PP00P1_128574, PP00P1_150739, and CRSII3_141965).

Financial Disclosures
Stefan Kaiser has received speaker honoraria from Roche, Lundbeck, Janssen and Takeda. He receives royalties for cognitive test and training software from Schuhfried. Erich Seifritz has received grant support from H. Lundbeck and has served as a consultant and/or speaker for AstraZeneca, Otsuka, Eli Lilly, Janssen, Lundbeck, Novartis, Pfizer, Roche, and Servier. None of these activities is related to the present study. All other authors declare no biomedical financial interests or potential conflicts of interest.

Appendix D: Curriculum Vitae

Personal Data

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2005 - 2012	University of Zurich, Master of Science Major: Psychology Minors: Biology, Business Administration
1999 - 2003	Kantonsschule Rämibühl, Matura Language profile (Italian, English, French)